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(54) Title: MAMMALIAN RECEPTOR PROTEINS; RELATED REAGENTS AND METHODS

(57) Abstract: Nucleic acids encoding mammalian, e.g., primate, receptors, purified receptor proteins and fragments thereof. Antibodies, both polyclonal and monoclonal, are also provided. Methods of using the compositions for both diagnostic and therapeutic utilities are described.

MAMMALIAN RECEPTOR PROTEINS; RELATED REAGENTS AND METHODS

This filing claims priority to U.S. Patent Application 09/443,060, filed November 18, 1999, and U.S. Application 60/170,320, filed December 13, 1999, each of which is incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates to compositions and methods for affecting mammalian physiology, including immune system function. In particular, it provides methods to regulate development and/or the immune system. Diagnostic and therapeutic uses of these materials are also disclosed.

BACKGROUND OF THE INVENTION

Recombinant DNA technology refers generally to techniques of integrating genetic information from a donor source into vectors for subsequent processing, such as through introduction into a host, whereby the transferred genetic information is copied and/or expressed in the new environment. Commonly, the genetic information exists in the form of complementary DNA (cDNA) derived from messenger RNA (mRNA) coding for a desired protein product. The carrier is frequently a plasmid having the capacity to incorporate cDNA for later replication in a host and, in some cases, actually to control expression of the cDNA and thereby direct synthesis of the encoded product in the host. See, e.g., Sambrook, et al. (1989) Molecular Cloning: A Laboratory Manual, (2d ed.) vols. 1-3, CSH Press, NY.

For some time, it has been known that the mammalian immune response is based on a series of complex cellular interactions, called the "immune network". Recent research has provided new insights into the inner workings of this network. While it remains clear that much of the immune response does, in fact, revolve around the network-like interactions of lymphocytes, macrophages, granulocytes, and other cells, immunologists now

generally hold the opinion that soluble proteins, known as lymphokines, cytokines, or monokines, play critical roles in controlling these cellular interactions. Thus, there is considerable interest in the isolation, characterization, and mechanisms of action of cell modulatory factors, an understanding of which will lead to significant advancements in the diagnosis and therapy of numerous medical abnormalities, e.g., immune system disorders.

Lymphokines apparently mediate cellular activities in a variety of ways. See, e.g., Paul (ed. 1996) Fundamental Immunology 3d ed., Raven Press, New York; and Thomson (ed. 1994) The Cytokine Handbook 2d ed., Academic Press, San Diego. They have been shown to support the proliferation, growth, and/or differentiation of pluripotential hematopoietic stem cells into vast numbers of progenitors comprising diverse cellular lineages which make up a complex immune system. Proper and balanced interactions between the cellular components are necessary for a healthy immune response. The different cellular lineages often respond in a different manner when lymphokines are administered in conjunction with other agents.

Cell lineages especially important to the immune response include two classes of lymphocytes: B-cells, which can produce and secrete immunoglobulins (proteins with the capability of recognizing and binding to foreign matter to effect its removal), and T-cells of various subsets that secrete lymphokines and induce or suppress the B-cells and various other cells (including other T-cells) making up the immune network. These lymphocytes interact with many other cell types.

Research to better understand and treat various immune disorders has been hampered by the general inability to maintain cells of the immune system in vitro. Immunologists have discovered that culturing many of these cells can be accomplished through the use of T-cell and other cell supernatants, which contain various growth factors, including many of the lymphokines.

Various growth and regulatory factors exist which modulate morphogenetic development. Many receptors for cytokines are

known. Often, there are at least two critical subunits in the functional receptor. See, e.g., Gonda and D'Andrea (1997) Blood 89:355-369; Presky, et al. (1996) Proc. Nat'l Acad. Sci. USA 93:14002-14007; Drachman and Kaushansky (1995) Curr. Opin. Hematol. 2:22-28; Theze (1994) Eur. Cytokine Netw. 5:353-368; and Lemmon and Schlessinger (1994) Trends Biochem. Sci. 19:459-463.

From the foregoing, it is evident that the discovery and development of new receptors, including ones similar to known receptors for lymphokines, should contribute to new therapies. In particular, the discovery and understanding of novel receptors for lymphokine-like molecules which enhance or potentiate the beneficial activities of other lymphokines would be highly advantageous. The present invention provides new receptors for ligands exhibiting similarity to cytokine like compositions and related compounds, and methods for their use.

SUMMARY OF THE INVENTION

The present invention is directed to novel receptors related to cytokine receptors, e.g., primate, cytokine receptor like molecular structures, designated DNAX Cytokine Receptor Subunits (DCRS), and their biological activities. In particular, it provides descriptions of subunits designated DCRS3 (referring to two embodiments designated DCRS3.1 and DCRS3.2) and DCRS4 (referring to three embodiments designated DCRS4.1, DCRS4.2, and DCRS4.3). It includes nucleic acids coding for the polypeptides themselves and methods for their production and use. The nucleic acids of the invention are characterized, in part, by their homology to cloned complementary DNA (cDNA) sequences enclosed herein.

The present invention provides a composition of matter selected from: a substantially pure or recombinant: DCRS3 polypeptide comprising: at least three distinct nonoverlapping segments of at least four amino acids identical to segments of SEQ ID NO: 2 or 25; a substantially pure or recombinant DCRS3 polypeptide comprising at least two distinct nonoverlapping segments of at least five amino acids identical to segments of

SEQ ID NO: 2 or 25; a natural sequence DCRS3 comprising mature SEQ ID NO: 2 or 25; a fusion polypeptide comprising DCRS3 sequence; or DCRS4 polypeptide comprising: at least three distinct nonoverlapping segments of at least four amino acids identical to segments of SEQ ID NO: 5, 28, or 31; a substantially pure or recombinant DCRS4 polypeptide comprising at least two distinct nonoverlapping segments of at least five amino acids identical to segments of SEQ ID NO: 5, 28, or 31; a natural sequence DCRS4 comprising mature SEQ ID NO: 5, 28, or 31; or a fusion polypeptide comprising DCRS4 sequence. In certain embodiments, the invention embraces such a substantially pure or isolated antigenic DCRS3 or DRS4 polypeptide, wherein the distinct nonoverlapping segments of identity: include one of at least eight amino acids; include one of at least four amino acids and a second of at least five amino acids; include at least three segments of at least four, five, and six amino acids, or include one of at least twelve amino acids. Other embodiments include wherein the: DCRS3 polypeptide: comprises a mature sequence of Table 1; is an unglycosylated form of DCRS3; is from a primate, such as a human; comprises at least seventeen amino acids of SEQ ID NO: 2 or 25; exhibits at least four nonoverlapping segments of at least seven amino acids of SEQ ID NO: 2 or 25; comprises a sequence of at least 3 amino acids on each side across an exon boundary; is a natural allelic variant of DCRS3; has a length at least about 30 amino acids; exhibits at least two non-overlapping epitopes which are specific for a primate DCRS3; is glycosylated; has a molecular weight of at least 30 kD with natural glycosylation; is a synthetic polypeptide; is attached to a solid substrate; is conjugated to another chemical moiety; is a 5-fold or less substitution from natural sequence; or is a deletion or insertion variant from a natural sequence; or DCRS4 polypeptide: comprises a mature sequence of Table 3; is an unglycosylated form of DCRS4; is from a primate, such as a human; comprises at least seventeen amino acids of SEQ ID NO: 5; exhibits at least four nonoverlapping segments of at least seven amino acids of SEQ ID NO: 5, 28, or 31; comprises a sequence of at least 3 amino acids on each side

across an exon boundary; is a natural allelic variant of DCRS5; has a length at least about 30 amino acids; exhibits at least two non-overlapping epitopes which are specific for a primate DCRS5; is glycosylated; has a molecular weight of at least 30 kD with natural glycosylation; is a synthetic polypeptide; is attached to a solid substrate; is conjugated to another chemical moiety; is a 5-fold or less substitution from natural sequence; or is a deletion or insertion variant from a natural sequence. Still other embodiments include a composition comprising: a substantially pure DCRS3 and another cytokine receptor family member; a sterile DCRS3 polypeptide; the DCRS3 polypeptide and a carrier, wherein the carrier is: an aqueous compound, including water, saline, and/or buffer; and/or formulated for oral, rectal, nasal, topical, or parenteral administration; a substantially pure DCRS4 and another cytokine receptor family member; a sterile DCRS4 polypeptide; the DCRS4 polypeptide and a carrier, wherein the carrier is: an aqueous compound, including water, saline, and/or buffer; and/or formulated for oral, rectal, nasal, topical, or parenteral administration. Fusion polypeptide embodiments include those comprising: mature protein sequence of Table 1 or 3; a detection or purification tag, including a FLAG, His6, or Ig sequence; or sequence of another interferon receptor protein. Kit embodiments include those comprising such a polypeptide, and: a compartment comprising the protein or polypeptide; or instructions for use or disposal of reagents in the kit.

Binding compound embodiments include, e.g., a binding compound comprising an antigen binding site from an antibody, which specifically binds to a natural: DCRS3 polypeptide, wherein: the binding compound is in a container; the DCRS3 polypeptide is from a human; the binding compound is an Fv, Fab, or Fab2 fragment; the binding compound is conjugated to another chemical moiety; or the antibody: is raised against a peptide sequence of a mature polypeptide of Table 1; is raised against a mature DCRS3; is raised to a purified human DCRS3; is immunoselected; is a polyclonal antibody; binds to a denatured DCRS3; exhibits a Kd to antigen of at least 30 μM; is attached

to a solid substrate, including a bead or plastic membrane; is in a sterile composition; or is detectably labeled, including a radioactive or fluorescent label; or DCRS4 polypeptide, wherein: the binding compound is in a container; the DCRS4 polypeptide is from a human; the binding compound is an Fv, Fab, or Fab2 fragment; the binding compound is conjugated to another chemical moiety; or the antibody: is raised against a peptide sequence of a mature polypeptide of Table 3; is raised against a mature DCRS4; is raised to a purified human DCRS4; is immunoselected; is a polyclonal antibody; binds to a denatured DCRS4; exhibits a Kd to antigen of at least 30 µM; is attached to a solid substrate, including a bead or plastic membrane; is in a sterile composition; or is detectably labeled, including a radioactive or fluorescent label. Kits include those comprising the binding compound, and: a compartment comprising the binding compound; or instructions for use or disposal of reagents in the kit.

Methods are provided, e.g., of producing an antigen:antibody complex, comprising contacting under appropriate conditions: a primate DCRS3 polypeptide with a described antibody, thereby allowing the complex to form; or a primate DCRS4 polypeptide with a described antibody, thereby allowing the complex to form. This includes wherein: the complex is purified from other cytokine receptors; the complex is purified from other antibody; the contacting is with a sample comprising another cytokine; the contacting allows quantitative detection of the antigen; the contacting is with a sample comprising the antibody; or the contacting allows quantitative detection of the antibody.

Various related compositions are provided, e.g., a composition comprising: a sterile binding compound, as described, or the described binding compound and a carrier, wherein the carrier is: an aqueous compound, including water, saline, and/or buffer; and/or formulated for oral, rectal, nasal, topical, or parenteral administration.

Nucleic acid embodiments include, e.g., an isolated or recombinant nucleic acid encoding the DCRS3 polypeptide, wherein the: DCRS3 is from a human; or the nucleic acid: encodes an

antigenic peptide sequence of Table 1; encodes a plurality of antigenic peptide sequences of Table 1; exhibits identity over at least thirteen nucleotides to a natural cDNA encoding the segment; is an expression vector; further comprises an origin of replication; is from a natural source; comprises a detectable label; comprises synthetic nucleotide sequence; is less than 6 kb, preferably less than 3 kb; is from a primate; comprises a natural full length coding sequence; is a hybridization probe for a gene encoding the DCRS3; or is a PCR primer, PCR product, or mutagenesis primer; or an isolated or recombinant nucleic acid encoding the DCRS4 polypeptide, wherein the: DCRS4 is from a human; or the nucleic acid: encodes an antigenic peptide sequence of Table 3; encodes a plurality of antigenic peptide sequences of Table 3; exhibits identity over at least thirteen nucleotides to a natural cDNA encoding the segment; is an expression vector; further comprises an origin of replication; is from a natural source; comprises a detectable label; comprises synthetic nucleotide sequence; is less than 6 kb, preferably less than 3 kb; is from a primate; comprises a natural full length coding sequence; is a hybridization probe for a gene encoding the DCRS4; or is a PCR primer, PCR product, or mutagenesis primer. Other embodiments of the invention include a cell or tissue comprising the described recombinant nucleic acid. Preferably, the cell is: a prokaryotic cell; a eukaryotic cell; a bacterial cell; a yeast cell; an insect cell; a mammalian cell; a mouse cell; a primate cell; or a human cell.

Kit embodiments include those comprising a described nucleic acid, and: a compartment comprising the nucleic acid; a compartment further comprising a primate DCRS3 or DCRS4 polypeptide; or instructions for use or disposal of reagents in the kit.

Alternative nucleic acid embodiments include a nucleic acid which: hybridizes under wash conditions of 30 minutes at 30° C and less than 2M salt to the coding portion of: SEQ ID NO: 1, 24, 4, 27, or 30; or exhibits identity over a stretch of at least about 30 nucleotides to a primate DCRS3 or DCRS4. Preferred embodiments include those wherein: the wash conditions

are at 45° C and/or 500 mM salt; the wash conditions are at 55° C and/or 150 mM salt; the stretch is at least 55 nucleotides; or the stretch is at least 75 nucleotides.

Other methods include those of modulating physiology or development of a cell or tissue culture cells comprising contacting the cell with an agonist or antagonist of a mammalian DCRS3 or DCRS4. Preferably, the cell is transformed with a nucleic acid encoding a DCRS3 or DCRS4 and another cytokine receptor subunit.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

OUTLINE

I. General
II. Activities
III. Nucleic acids
    A. encoding fragments, sequence, probes
    B. mutations, chimeras, fusions
    C. making nucleic acids
    D. vectors, cells comprising
IV. Proteins, Peptides
    A. fragments, sequence, immunogens, antigens
    B. muteins
    C. agonists/antagonists, functional equivalents
    D. making proteins
V. Making nucleic acids, proteins
    A. synthetic
    B. recombinant
    C. natural sources
VI. Antibodies
    A. polyclonals
    B. monoclonal
    C. fragments; Kd
    D. anti-idiotypic antibodies
    E. hybridoma cell lines
VII. Kits and Methods to quantify DCRS
    A. ELISA
    B. assay mRNA encoding
    C. qualitative/quantitative
    D. kits
VIII. Therapeutic compositions, methods
    A. combination compositions
    B. unit dose
    C. administration
IX. Screening

X. Ligands

I. General

The present invention provides the amino acid sequences and DNA sequences of mammalian, herein primate, cytokine receptor-like subunit molecules, these designated DNAX Cytokine Receptor Subunit 3 (DCRS3; 50R) and DNAX Cytokine Receptor Subunit 4 (DCRS4; cytor) having particular defined properties, both structural and biological. Various cDNAs encoding these molecules were obtained from primate, e.g., human, cDNA sequence libraries. Other primate or other mammalian counterparts would also be desired.

Some of the standard methods applicable are described or referenced, e.g., in Maniatis, et al. (1982) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Laboratory, Cold Spring Harbor Press; Sambrook, et al. (1989) Molecular Cloning: A Laboratory Manual, (2d ed.), vols. 1-3, CSH Press, NY; Ausubel, et al., Biology, Greene Publishing Associates, Brooklyn, NY; or Ausubel, et al. (1987 and periodic supplements) Current Protocols in Molecular Biology, Greene/Wiley, New York; each of which is incorporated herein by reference.

Nucleotide (SEQ ID NO: 1) and corresponding amino acid sequence (SEQ ID NO: 2) of a human DCRS3 coding segment are shown in Table 1; likewise for the DCRS3.2 as SEQ ID NO: 24 and 25; comparison of DCRS3.1 and DCRS3.2 polypeptide sequences is shown also in Table 1. Reverse translations based upon the universal genetic code are provided in Table 2; comparison of the encoding nucleic acid sequences is also presented in Table 2. The sequences are derived from genomic sequence at chromosome location clones CIT987SK-582J2 HUAC004525 and CIT987-SKA-670B5 HUAC002303, at 16p12, and other cDNA sequences. The predicted signal sequence is indicated, but may depend on cell type, or may be a few residues in either direction. The transmembrane segment (SEQ ID NO: 2) is predicted to run from about leu248-ser264 (glu242-his268). Predicted fibronectin domain runs from about asn128-tyr220; cytokine receptor WS box from about trp224-ser228; conserved disulfide motif between

cys6-cys26; second conserved disulfide linkage at cys65-cys89; five N glycosylation sites at Asn residues 61, 97, 121, 128, and 145; seven cAMP PK sites at lys4; lys68; lys184; arg191; arg201; lys202; and lys292; fourteen Ca phosphorylation sites at thr71, ser130, ser187, ser205, ser237, ser182, ser195, ser310, ser317, thr323, ser374, ser385, ser403, and thr499; five myristoly sites at gly174, gly303, gly439, gly449, and gly466; four PKC phosphorylation sites at ser7, ser147, ser180, and ser264; and one tyrosine kinase site at lys163.

Exon boundaries are predicted to be about between nucleotides g49-c50, g230-g231, g284-g285, a484-g485, g597-a598, g775-a776, g875-g876, and g957-a958. Because the sequences have been derived from genomic sequence, in which the introns have not been spliced out, particularly important compositions will be those which encode segments across the boundaries, e.g., both nucleic acid sequence and amino acid sequence. The segments will comprise, e.g., segments across the boundary which may comprise 8, 9, 11, 13, 15, 17 20, 25, 30, 35, 50, or more nucleotides on either or both sides adjacent to an exon boundary, or 4, 5, 6, 7, or 8 amino acids on either or both sides adjacent a boundary. The lengths on either side need not be the same for purposes of novelty, e.g., three amino acids on one side and 5 on the other side. Thus, e.g., compositions are provided comprising, e.g, 15 contiguous nucleotides across a boundary, of which at least 6 are from each side. Similarly, compositions are provided, e.g., comprising at least 3 amino acids from each side of the exon boundary, with a matching of at least 8 amino acids across the boundary. Also provided are compositions comprising a plurality of such segments across multiple exon boundaries, which different segments need not have the same length limitations. Thus, the invention provides a nucleic acid comprising, e.g., at least 5 nucleotides in each side across the exon 1/2 boundary, and at least 4 nucleotides on either side of the the exon 3/4, 4/5, 5/6, and/or 6/7 boundaries. Natural sequence compositions would be preferred.

Nucleotide (SEQ ID NO: 4) and corresponding amino acid sequence (SEQ ID NO: 5) of a human DCRS4 coding segment are

shown in Table 3; likewise for the DCRS4.2 as SEQ ID NO: 27 and 28 and the DCRS4.3 as SEQ ID NO: 30 and 31; comparison of DCRS4 polypeptide sequences is shown also in Table 3. Reverse translations based upon the universal genetic code are provided in Table 4; comparison of the encoding nucleic acid sequences is also presented in Table 4. The sequence of DCRS4.1 is derived from genomic sequence at chromosome location 6q24.1-25.2, within some 50 kb of IFNγR1 chain. The predicted DCRS4.1 signal sequence is indicated, but may depend on cell type, or may be a few residues in either direction. This embodiment of the receptor lacks a transmembrane segment, which is unusual, but there is precedent for soluble forms of cytokine receptor subunits. See, e.g, IL-12Rα (p40 subunit) and the EBI3 receptor subunit homolog. For the DCRS4.1, the predicted cytokine receptor domain from pro10-arg49; conserved disulfide motif between cys57-cys65; five N glycosylation sites at Asn residues 35, 131, 136, 157, and 174; four cAMP PK sites at arg30, lys98, lys106, and lys156; eight Ca phosphorylation sites at thr4, thr60, ser64, thr68, thr71, ser159, ser176, and ser220; three myristoly sites at gly89, gly103, and gly186; three PKC phosphorylation sites at ser7, ser97, and ser217; one amidation site at tyr79; one cAMP phosphorylation site at lys98; and two CK2 phosphorylation sites at ser3 and ser159. Exon boundaries are predicted to be about between nucleotides c59-a60; t197-a198, g206-a207, g430-c431, and g601-a602. Alignment with the other DCRS4 embodiments is provided. As described above, compositions with sequence across the exon boundaries are provided.

Table 1: Nucleotide and polypeptide sequences of DNAX Cytokine Receptor Subunit like embodiments (DCRS3.1; 50R). Primate, e.g., human embodiment (see SEQ ID NO: 1 and 2). Predicted signal sequence indicated, but may vary by a few positions and depending upon cell type.

```
atg ccg cgt ggc tgg gcc gcc ccc ttg ctc ctg ctg ctg ctc cag gga    48
Met Pro Arg Gly Trp Ala Ala Pro Leu Leu Leu Leu Leu Leu Gln Gly
-20                 -15                 -10                  -5

gcc ctc gag ggg atg gag agg aag ctc tgc agt ccc aag cca ccc ccc    96
Ala Leu Glu Gly Met Glu Arg Lys Leu Cys Ser Pro Lys Pro Pro Pro
             -1   1              5                  10

acc aag gcc tct ctc ccc act gac cct cca ggc tgg ggc tgc ccc gac   144
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Thr Lys Ala Ser Leu Pro Thr Asp Pro Pro Gly Trp Gly Cys Pro Asp
        15                  20                  25

ctc gtc tgc tac acc gat tac ctc cag acg gtc atc tgc atc ctg gaa     192
Leu Val Cys Tyr Thr Asp Tyr Leu Gln Thr Val Ile Cys Ile Leu Glu
    30                  35                  40

atg tgg aac ctc cac ccc agc acg ctc acc ctt acc tgg ata ctt tct     240
Met Trp Asn Leu His Pro Ser Thr Leu Thr Leu Thr Trp Ile Leu Ser
45                  50                  55                  60

aat aat act ggg tgc tat atc aag gac aga aca ctg gac ctc agg caa     288
Asn Asn Thr Gly Cys Tyr Ile Lys Asp Arg Thr Leu Asp Leu Arg Gln
                65                  70                  75

gac cag tat gaa gag ctg aag gac gag gcc acc tcc tgc agc ctc cac     336
Asp Gln Tyr Glu Glu Leu Lys Asp Glu Ala Thr Ser Cys Ser Leu His
            80                  85                  90

agg tcg gcc cac aat gcc acg cat gcc acc tac acc tgc cac atg gat     384
Arg Ser Ala His Asn Ala Thr His Ala Thr Tyr Thr Cys His Met Asp
        95                  100                 105

gta ttc cac ttc atg gcc gac gac att ttc agt gtc aac atc aca gac     432
Val Phe His Phe Met Ala Asp Asp Ile Phe Ser Val Asn Ile Thr Asp
    110                 115                 120

cag tct ggc aac tac tcc cag gag tgt ggc agc ttt ctc ctg gct gag     480
Gln Ser Gly Asn Tyr Ser Gln Glu Cys Gly Ser Phe Leu Leu Ala Glu
125                 130                 135                 140

agc aga cag tat aat atc tcc tgg cgc tca gat tac gaa gac cct gcc     528
Ser Arg Gln Tyr Asn Ile Ser Trp Arg Ser Asp Tyr Glu Asp Pro Ala
                145                 150                 155

ttc tac atg ctg aag ggc aag ctt cag tat gag ctg cag tac agg aac     576
Phe Tyr Met Leu Lys Gly Lys Leu Gln Tyr Glu Leu Gln Tyr Arg Asn
            160                 165                 170

cgg gga gac ccc tgg gct gtg agt ccg agg aga aag ctg atc tca gtg     624
Arg Gly Asp Pro Trp Ala Val Ser Pro Arg Arg Lys Leu Ile Ser Val
        175                 180                 185

gac tca aga agt gtc tcc ctc ctc ccc ctg gag ttc cgc aaa gac tcg     672
Asp Ser Arg Ser Val Ser Leu Leu Pro Leu Glu Phe Arg Lys Asp Ser
    190                 195                 200

agc tat gag ctg cag gtg cgg gca ggg ccc atg cct ggc tcc tcc tac     720
Ser Tyr Glu Leu Gln Val Arg Ala Gly Pro Met Pro Gly Ser Ser Tyr
205                 210                 215                 220

cag ggg acc tgg agt gaa tgg agt gac ccg gtc atc ttt cag acc cag     768
Gln Gly Thr Trp Ser Glu Trp Ser Asp Pro Val Ile Phe Gln Thr Gln
                225                 230                 235

tca gag gag tta aag gaa ggc tgg aac cct cac ctg ctg ctt ctc ctc     816
Ser Glu Glu Leu Lys Glu Gly Trp Asn Pro His Leu Leu Leu Leu Leu
            240                 245                 250

ctg ctt gtc ata gtc ttc att cct gcc ttc tgg agc ctg aag acc cat     864
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Leu Leu Val Ile Val Phe Ile Pro Ala Phe Trp Ser Leu Lys Thr His
        255                 260                 265

cca ttg tgg agg cta tgg aag aag ata tgg gcc gtc ccc agc cct gag     912
Pro Leu Trp Arg Leu Trp Lys Lys Ile Trp Ala Val Pro Ser Pro Glu
    270                 275                 280

cgg ttc ttc atg ccc ctg tac aag ggc tgc agc gga gac ttc aag aaa     960
Arg Phe Phe Met Pro Leu Tyr Lys Gly Cys Ser Gly Asp Phe Lys Lys
285                 290                 295                 300

tgg gtg ggt gca ccc ttc act ggc tcc agc ctg gag ctg gga ccc tgg    1008
Trp Val Gly Ala Pro Phe Thr Gly Ser Ser Leu Glu Leu Gly Pro Trp
                305                 310                 315

agc cca gag gtg ccc tcc acc ctg gag gtg tac agc tgc cac cca cca    1056
Ser Pro Glu Val Pro Ser Thr Leu Glu Val Tyr Ser Cys His Pro Pro
            320                 325                 330

cgg agc ccg gcc aag agg ctg cag ctc acg gag cta caa gaa cca gca    1104
Arg Ser Pro Ala Lys Arg Leu Gln Leu Thr Glu Leu Gln Glu Pro Ala
        335                 340                 345

gag ctg gtg gag tct gac ggt gtg ccc aag ccc agc ttc tgg ccg aca    1152
Glu Leu Val Glu Ser Asp Gly Val Pro Lys Pro Ser Phe Trp Pro Thr
    350                 355                 360

gcc cag aac tcg ggg ggc tca gct tac agt gag gag agg gat cgg cca    1200
Ala Gln Asn Ser Gly Gly Ser Ala Tyr Ser Glu Glu Arg Asp Arg Pro
365                 370                 375                 380

tac ggc ctg gtg tcc att gac aca gtg act gtg cta gat gca gag ggg    1248
Tyr Gly Leu Val Ser Ile Asp Thr Val Thr Val Leu Asp Ala Glu Gly
                385                 390                 395

cca tgc acc tgg ccc tgc agc tgt gag gat gac ggc tac cca gcc ctg    1296
Pro Cys Thr Trp Pro Cys Ser Cys Glu Asp Asp Gly Tyr Pro Ala Leu
            400                 405                 410

gac ctg gat gct ggc ctg gag ccc agc cca ggc cta gag gac cca ctc    1344
Asp Leu Asp Ala Gly Leu Glu Pro Ser Pro Gly Leu Glu Asp Pro Leu
        415                 420                 425

ttg gat gca ggg acc aca gtc ctg tcc tgt ggc tgt gtc tca gct ggc    1392
Leu Asp Ala Gly Thr Thr Val Leu Ser Cys Gly Cys Val Ser Ala Gly
    430                 435                 440

agc cct ggg cta gga ggg ccc ctg gga agc ctc ctg gac aga cta aag    1440
Ser Pro Gly Leu Gly Gly Pro Leu Gly Ser Leu Leu Asp Arg Leu Lys
445                 450                 455                 460

cca ccc ctt gca gat ggg gag gac tgg gct ggg gga ctg ccc tgg ggt    1488
Pro Pro Leu Ala Asp Gly Glu Asp Trp Ala Gly Gly Leu Pro Trp Gly
                465                 470                 475
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ggc cgg tca cct gga ggg gtc tca gag agt gag gcg ggc tca ccc ctg    1536
Gly Arg Ser Pro Gly Gly Val Ser Glu Ser Glu Ala Gly Ser Pro Leu
            480                 485                 490

gcc ggc ctg gat atg gac acg ttt gac agt ggc ttt gtg ggc tct gac    1584
Ala Gly Leu Asp Met Asp Thr Phe Asp Ser Gly Phe Val Gly Ser Asp
        495                 500                 505

tgc agc agc cct gtg gag tgt gac ttc acc agc ccc ggg gac gaa gga    1632
Cys Ser Ser Pro Val Glu Cys Asp Phe Thr Ser Pro Gly Asp Glu Gly
    510                 515                 520

ccc ccc cgg agc tac ctc cgc cag tgg gtg gtc att cct ccg cca ctt    1680
Pro Pro Arg Ser Tyr Leu Arg Gln Trp Val Val Ile Pro Pro Pro Leu
525                 530                 535                 540

tcg agc cct gga ccc cag gcc agc taa                                1707
Ser Ser Pro Gly Pro Gln Ala Ser
                545
```

MPRGWAAPLLLLLLQGALEGMERKLCSPKPPPTKASLPTDPPGWGCPDLVCYTDYLQTVICILEMWNLHPSTLTLTW
ILSNNTGCYIKDRTLDLRQDQYEELKDEATSCSLHRSAHNATHATYTCHMDVFHFMADDIFSVNITDQSGNYSQECG
SFLLAESRQYNISWRSDYEDPAFYMLKGKLQYELQYRNRGDPWAVSPRRKLISVDSRSVSLLPLEFRKDSSYELQVR
AGPMPGSSYQGTWSEWSDPVIFQTQSEELKEGWNPHLLLLLLLVIVFIPAFWSLKTHPLWRLWKKIWAVPSPERFFM
PLYKGCSGDFKKWVGAPFTGSSLELGPWSPEVPSTLEVYSCHPPRSPAKRLQLTELQEPAELVESDGVPKPSFWPTA
QNSGGSAYSEERDRPYGLVSIDTVTVLDAEGPCTWPCSCEDDGYPALDLDAGLEPSPGLEDPLLDAGTTVLSCGCVS
AGSPGLGGPLGSLLDRLKPPLADGEDWAGGLPWGGRSPGGVSESEAGSPLAGLDMDTFDSGFVGSDCSSPVECDFTS
PGDEGPPRSYLRQWVVIPPPLSSPGPQAS

Nucleotide and polypeptide sequences of DNAX Cytokine Receptor Subunit like embodiments (DCRS3.2; SEQ ID NO: 24 and 25):

```
atg ccg cgt ggc tgg gcc gcc ccc ttg ctc ctg ctg ctg ctc cag gga    48
Met Pro Arg Gly Trp Ala Ala Pro Leu Leu Leu Leu Leu Leu Gln Gly
-20                 -15                 -10                 -5

ggc tgg ggc tgc ccc gac ctc gtc tgc tac acc gat tac ctc cag acg    96
Gly Trp Gly Cys Pro Asp Leu Val Cys Tyr Thr Asp Tyr Leu Gln Thr
            -1   1               5                  10

gtc atc tgc atc ctg gaa atg tgg aac ctc cac ccc agc acg ctc acc    144
Val Ile Cys Ile Leu Glu Met Trp Asn Leu His Pro Ser Thr Leu Thr
        15                  20                  25

ctt acc tgg caa gac cag tat gaa gag ctg aag gac gag gcc acc tcc    192
Leu Thr Trp Gln Asp Gln Tyr Glu Glu Leu Lys Asp Glu Ala Thr Ser
    30                  35                  40

tgc agc ctc cac agg tcg gcc cac aat gcc acg cat gcc acc tac acc    240
Cys Ser Leu His Arg Ser Ala His Asn Ala Thr His Ala Thr Tyr Thr
45                  50                  55                  60

tgc cac atg gat gta ttc cac ttc atg gcc gac gac att ttc agt gtc    288
Cys His Met Asp Val Phe His Phe Met Ala Asp Asp Ile Phe Ser Val
                65                  70                  75

aac atc aca gac cag tct ggc aac tac tcc cag gan tgt ggc agc ttt    336
Asn Ile Thr Asp Gln Ser Gly Asn Tyr Ser Gln Xaa Cys Gly Ser Phe
            80                  85                  90
```

```
ctc ctg gct gag agc atc aag ccg gct ccc cct ttc aac gtg act gtg     384
Leu Leu Ala Glu Ser Ile Lys Pro Ala Pro Pro Phe Asn Val Thr Val
         95                 100                 105

acc ttc tca gga cag tat aat atn tcc tgg cgc tca gat tac gaa gac     432
Thr Phe Ser Gly Gln Tyr Asn Xaa Ser Trp Arg Ser Asp Tyr Glu Asp
    110                 115                 120

cct gcc ttc tac atg ctg aaa ggc aag ctt caa tat gag ctg cag tac     480
Pro Ala Phe Tyr Met Leu Lys Gly Lys Leu Gln Tyr Glu Leu Gln Tyr
125                 130                 135                 140

agg aac cgg gga gac ccc tgg gct gtg agt ccg agg aga aag ctg atc     528
Arg Asn Arg Gly Asp Pro Trp Ala Val Ser Pro Arg Arg Lys Leu Ile
                145                 150                 155

tca gtg gac tca aga agt gtc tcc ctc ctc ccc ctg gag ttc cgc aaa     576
Ser Val Asp Ser Arg Ser Val Ser Leu Leu Pro Leu Glu Phe Arg Lys
            160                 165                 170

gac tcg agc tat gag ctg can gtg cgg gca ggg ccc atg cct ggc tcc     624
Asp Ser Ser Tyr Glu Leu Xaa Val Arg Ala Gly Pro Met Pro Gly Ser
        175                 180                 185

tcc tac cag ggg acc tgg agt gaa tgg agt gac ccg gtc atc tgt cag     672
Ser Tyr Gln Gly Thr Trp Ser Glu Trp Ser Asp Pro Val Ile Cys Gln
    190                 195                 200

acc cag tca gag gag tta aag gaa ggc tgg aac cct cac ctg ctg ctt     720
Thr Gln Ser Glu Glu Leu Lys Glu Gly Trp Asn Pro His Leu Leu Leu
205                 210                 215                 220

ctc ctc ctg ctt gtc ata gtc ttc att cct gcc ttc tgg agc ctg aag     768
Leu Leu Leu Leu Val Ile Val Phe Ile Pro Ala Phe Trp Ser Leu Lys
                225                 230                 235

acc cat cca ttg tgg agg cta tgg aag aag ata tgg gcc gtc ccc agc     816
Thr His Pro Leu Trp Arg Leu Trp Lys Lys Ile Trp Ala Val Pro Ser
            240                 245                 250

cct gag cgg ttc ttc atg ccc ctg tac aag ggc tgc agc gga gac ttc     864
Pro Glu Arg Phe Phe Met Pro Leu Tyr Lys Gly Cys Ser Gly Asp Phe
        255                 260                 265

aag aaa tgg gtg ggt gca ccc ttc act ggc tcc agc ctg gag ctg gga     912
Lys Lys Trp Val Gly Ala Pro Phe Thr Gly Ser Ser Leu Glu Leu Gly
    270                 275                 280

ccc tgg agc cca gag gtg ccc tcc acc ctg gag gtg tac agc tgc cac     960
Pro Trp Ser Pro Glu Val Pro Ser Thr Leu Glu Val Tyr Ser Cys His
285                 290                 295                 300

cca cca cgg agc ccg gcc aag agg ctg cag ctc acg gag cta caa gaa    1008
Pro Pro Arg Ser Pro Ala Lys Arg Leu Gln Leu Thr Glu Leu Gln Glu
                305                 310                 315
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cca gca gag ctg gtg gag tct gac ggt gtg ccc aag ccc agc ttc tgg    1056
Pro Ala Glu Leu Val Glu Ser Asp Gly Val Pro Lys Pro Ser Phe Trp
        320                 325                 330

ccg aca gcc cag aac tcg ggg ggc tca gct tac agt gag gag agg gat    1104
Pro Thr Ala Gln Asn Ser Gly Gly Ser Ala Tyr Ser Glu Glu Arg Asp
    335                 340                 345

cgg cca tac ggc ctg gtg tcc att gac aca gtg act gtg cta gat gca    1152
Arg Pro Tyr Gly Leu Val Ser Ile Asp Thr Val Thr Val Leu Asp Ala
    350                 355                 360

gag ggg cca tgc acc tgg ccc tgc agc tgt gag gat gac ggc tac cca    1200
Glu Gly Pro Cys Thr Trp Pro Cys Ser Cys Glu Asp Asp Gly Tyr Pro
365                 370                 375                 380

gcc ctg gac ctg gat gct ggc ctg gag ccc agc cca ggc cta gag gac    1248
Ala Leu Asp Leu Asp Ala Gly Leu Glu Pro Ser Pro Gly Leu Glu Asp
                385                 390                 395

cca ctc ttg gat gca ggg acc aca gtc ctg tcc tgt ggc tgt gtc tca    1296
Pro Leu Leu Asp Ala Gly Thr Thr Val Leu Ser Cys Gly Cys Val Ser
            400                 405                 410

gct ggc agc cct ggg cta gga ggg ccc ctg gga agc ctc ctg gac aga    1344
Ala Gly Ser Pro Gly Leu Gly Gly Pro Leu Gly Ser Leu Leu Asp Arg
        415                 420                 425

cta aag cca ccc ctt gca gat ggg gag gac tgg gct ggg gga ctg ccc    1392
Leu Lys Pro Pro Leu Ala Asp Gly Glu Asp Trp Ala Gly Gly Leu Pro
    430                 435                 440

tgg ggt ggc cgg tca cct gga ggg gtc tca gag agt gag gcg ggc tca    1440
Trp Gly Gly Arg Ser Pro Gly Gly Val Ser Glu Ser Glu Ala Gly Ser
445                 450                 455                 460

ccc ctg gcc ggc ctg gat atg gac acg ttt gac agt ggc ttt gtg ggc    1488
Pro Leu Ala Gly Leu Asp Met Asp Thr Phe Asp Ser Gly Phe Val Gly
                465                 470                 475

tct gac tgc agc agc cct gtg gag tgt gac ttc acc agc ccc ggg gac    1536
Ser Asp Cys Ser Ser Pro Val Glu Cys Asp Phe Thr Ser Pro Gly Asp
            480                 485                 490

gaa gga ccc ccc cgg agc tac ctc cgc cag tgg gtg gtc att cct ccg    1584
Glu Gly Pro Pro Arg Ser Tyr Leu Arg Gln Trp Val Val Ile Pro Pro
        495                 500                 505

cca ctt tcg agc cct gga ccc cag gcc agc taa                        1617
Pro Leu Ser Ser Pro Gly Pro Gln Ala Ser
    510                 515
```

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MPRGWAAPLLLLLLQGGWGCPDLVCYTDYLQTVICILEMWNLHPSTLTLTWQDQYEELKDEATSCSLHRSAHNATHA
TYTCHMDVFHFMADDIFSVNITDQSGNYSQXCGSFLLAESIKPAPPFNVTVTFSGQYNXSWRSDYEDPAFYMLKGKL
QYELQYRNRGDPWAVSPRRKLISVDSRSVSLLPLEFRKDSSYELXVRAGPMPGSSYQGTWSEWSDPVICQTQSEELK
EGWNPHLLLLLLLVIVFIPAFWSLKTHPLWRLWKKIWAVPSPERFFMPLYKGCSGDFKKWVGAPFTGSSLELGPWSP
EVPSTLEVYSCHPPRSPAKRLQLTELQEPAELVESDGVPKPSFWPTAQNSGGSAYSEERDRPYGLVSIDTVTVLDAE
```

GPCTWPCSCEDDGYPALDLDAGLEPSPGLEDPLLDAGTTVLSCGCVSAGSPGLGGPLGSLLDRLKPPLADGEDWAGG
LPWGGRSPGGVSESEAGSPLAGLDMDTFDSGFVGSDCSSPVECDFTSPGDEGPPRSYLRQWVVIPPPLSSPGPQAS

Polypeptide sequence comparison of DCRS3.2 and DCRS3.1:

```
DCRS3.2    1 MPRGWAAPLLLLLLQG--------------------------GWGCPDLV  24
DCRS3.1    1 MPRGWAAPLLLLLLQGALEGMERKLCSPKPPPTKASLPTDPPGWGCPDLV  50
             ****************                          ********

DCRS3.2   25 CYTDYLQTVICILEMWNLHPSTLTLTW------------------QDQYE  56
DCRS3.1   51 CYTDYLQTVICILEMWNLHPSTLTLTWILSNNTGCYIKDRTLDLRQDQYE 100
             ***************************                  *****

DCRS3.2   57 ELKDEATSCSLHRSAHNATHATYTCHMDVFHFMADDIFSVNITDQSGNYS 106
DCRS3.1  101 ELKDEATSCSLHRSAHNATHATYTCHMDVFHFMADDIFSVNITDQSGNYS 150
             **************************************************

DCRS3.2  107 QXCGSFLLAESIKPAPPFNVTVTFSGQYNXSWRSDYEDPAFYMLKGKLQY 156
DCRS3.1  151 QECGSFLLAE--------------SRQYNISWRSDYEDPAFYMLKGKLQY 186
             * ********              * *** ********************

DCRS3.2  157 ELQYRNRGDPWAVSPRRKLISVDSRSVSLLPLEFRKDSSYELXVRAGPMP 206
DCRS3.1  187 ELQYRNRGDPWAVSPRRKLISVDSRSVSLLPLEFRKDSSYELQVRAGPMP 236
             ****************************************** *******

DCRS3.2  207 GSSYQGTWSEWSDPVICQTQSEELKEGWNPHLLLLLLLVIVFIPAFWSLK 256
DCRS3.1  237 GSSYQGTWSEWSDPVIFQTQSEELKEGWNPHLLLLLLLVIVFIPAFWSLK 286
             **************** *********************************

DCRS3.2  257 THPLWRLWKKIWAVPSPERFFMPLYKGCSGDFKKWVGAPFTGSSLELGPW 306
DCRS3.1  287 THPLWRLWKKIWAVPSPERFFMPLYKGCSGDFKKWVGAPFTGSSLELGPW 336
             **************************************************

DCRS3.2  307 SPEVPSTLEVYSCHPPRSPAKRLQLTELQEPAELVESDGVPKPSFWPTAQ 356
DCRS3.1  337 SPEVPSTLEVYSCHPPRSPAKRLQLTELQEPAELVESDGVPKPSFWPTAQ 386
             **************************************************

DCRS3.2  357 NSGGSAYSEERDRPYGLVSIDTVTVLDAEGPCTWPCSCEDDGYPALDLDA 406
DCRS3.1  387 NSGGSAYSEERDRPYGLVSIDTVTVLDAEGPCTWPCSCEDDGYPALDLDA 436
             **************************************************

DCRS3.2  407 GLEPSPGLEDPLLDAGTTVLSCGCVSAGSPGLGGPLGSLLDRLKPPLADG 456
DCRS3.1  437 GLEPSPGLEDPLLDAGTTVLSCGCVSAGSPGLGGPLGSLLDRLKPPLADG 486
             **************************************************

DCRS3.2  457 EDWAGGLPWGGRSPGGVSESEAGSPLAGLDMDTFDSGFVGSDCSSPVECD 506
DCRS3.1  487 EDWAGGLPWGGRSPGGVSESEAGSPLAGLDMDTFDSGFVGSDCSSPVECD 536
             **************************************************

DCRS3.2  507 FTSPGDEGPPRSYLRQWVVIPPPLSSPGPQAS 538
DCRS3.1  537 FTSPGDEGPPRSYLRQWVVIPPPLSSPGPQAS 568
             ********************************
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Table 2: Reverse Translation of primate, e.g., human, DCRS3.1 (SEQ ID NO: 3). N may be A, C, G, or T.

ATGCCNMGNGGNTGGGCNGCNCCNYTNYTNYTNYTNYTNYTNCARGGNGCNYTNGARGGNATGGARMGNAARYTNTG
YWSNCCNAARCCNCCNCCNACNAARGCNWSNYTNCCNACNGAYCCNCCNGGNTGGGGNTGYCCNGAYYTNGTNTGYT
AYACNGAYTAYYTNCARACNGTNATHTGYATHYTNGARATGTGGAAYYTNCAYCCNWSNACNYTNACNYTNACNTGG
ATHYTNWSNAAYAAYACNGGNTGYTAYATHAARGAYMGNACNYTNGAYYTNMGNCARGAYCARTAYGARGARYTNAA

RGAYGARGCNACNWSNTGYWSNYTNCAYMGNWSNGCNCAYAAYGCNACNCAYGCNACNTAYACNTGYCAYATGGAYG
TNTTYCAYTTYATGGCNGAYGAYATHTTYWSNGTNAAYATHACNGAYCARWSNGGNAAYTAYWSNCARGARTGYGGN
WSNTTYYTNYTNGCNGARWSNMGNCARTAYAAYATHWSNTGGMGNWSNGAYTAYGARGAYCCNGCNTTYTAYATGYT
NAARGGNAARYTNCARTAYGARYTNCARTAYMGNAAYMGNGGNGAYCCNTGGGCNGTNWSNCCNMGNMGNAARYTNA
THWSNGTNGAYWSNMGNWSNGTNWSNYTNYTNCCNYTNGARTTYMGNAARGAYWSNWSNTAYGARYTNCARGTNMGN
GCNGGNCCNATGCCNGGNWSNWSNTAYCARGGNACNTGGWSNGARTGGWSNGAYCCNGTNATHTTYCARACNCARWS
NGARGARYTNAARGARGGNTGGAAYCCNCAYYTNYTNYTNYTNYTNYTNYTNGTNATHGTNTTYATHCCNGCNTTYT
GGWSNYTNAARACNCAYCCNYTNTGGMGNYTNTGGAARAARATHTGGGCNGTNCCNWSNCCNGARMGNTTYTTYATG
CCNYTNTAYAARGGNTGYWSNGGNGAYTTYAARAARTGGGTNGGNGCNCCNTTYACNGGNWSNWSNYTNGARYTNGG
NCCNTGGWSNCCNGARGTNCCNWSNACNYTNGARGTNTAYWSNTGYCAYCCNCCNMGNWSNCCNGCNAARMGNYTNC
ARYTNACNGARYTNCARGARCCNGCNGARYTNGTNGARWSNGAYGGNGTNCCNAARCCNWSNTTYTGGCCNACNGCN
CARAAYWSNGGNGGNWSNGCNTAYWSNGARGARMGNGAYMGNCCNTAYGGNYTNGTNWSNATHGAYACNGTNACNGT
NYTNGAYGCNGARGGNCCNTGYACNTGGCCNTGYWSNTGYGARGAYGAYGGNTAYCCNGCNYTNGAYYTNGAYGCNG
GNYTNGARCCNWSNCCNGGNYTNGARGAYCCNYTNYTNGAYGCNGGNACNACNGTNYTNWSNTGYGGNTGYGTNWSN
GCNGGNWSNCCNGGNYTNGGNGGNCCNYTNGGNWSNYTNYTNGAYMGNYTNAARCCNCCNYTNGCNGAYGGNGARGA
YTGGGCNGGNGGNYTNCCNTGGGGNGGNMGNWSNCCNGGNGGNGTNWSNGARWSNGARGCNGGNWSNCCNYTNGCNG
GNYTNGAYATGGAYACNTTYGAYWSNGGNTTYGTNGGNWSNGAYTGYWSNWSNCCNGTNGARTGYGAYTTYACNWSN
CCNGGNGAYGARGGNCCNCCNMGNWSNTAYYTNMGNCARTGGGTNGTNATHCCNCCNCCNYTNWSNWSNCCNGGNCC
NCARGCNWSN

Reverse Translation of primate, e.g., human, DCRS3.2 (SEQ ID NO: 26). N may be A, C, G, or T.

ATGCCNMGNGGNTGGGCNGCNCCNYTNYTNYTNYTNYTNYTNCARGGNGGNTGGGGNTGYCCNGAYYTNGTNTGYTA
YACNGAYTAYYTNCARACNGTNATHTGYATHYTNGARATGTGGAAYYTNCAYCCNWSNACNYTNACNYTNACNTGGC
ARGAYCARTAYGARGARYTNAARGAYGARGCNACNWSNTGYWSNYTNCAYMGNWSNGCNCAYAAYGCNACNCAYGCN
ACNTAYACNTGYCAYATGGAYGTNTTYCAYTTYATGGCNGAYGAYATHTTYWSNGTNAAYATHACNGAYCARWSNGG
NAAYTAYWSNCARNNNTGYGGNWSNTTYYTNYTNGCNGARWSNATHAARCCNGCNCCNCCNTTYAAYGTNACNGTNA
CNTTYWSNGGNCARTAYAAYNNNWSNTGGMGNWSNGAYTAYGARGAYCCNGCNTTYTAYATGYTNAARGGNAARYTN
CARTAYGARYTNCARTAYMGNAAYMGNGGNGAYCCNTGGGCNGTNWSNCCNMGNMGNAARYTNATHWSNGTNGAYWS
NMGNWSNGTNWSNYTNYTNCCNYTNGARTTYMGNAARGAYWSNWSNTAYGARYTNNNNGTNMGNGCNGGNCCNATGC
CNGGNWSNWSNTAYCARGGNACNTGGWSNGARTGGWSNGAYCCNGTNATHTGYCARACNCARWSNGARGARYTNAAR
GARGGNTGGAAYCCNCAYYTNYTNYTNYTNYTNYTNYTNGTNATHGTNTTYATHCCNGCNTTYTGGWSNYTNAARAC
NCAYCCNYTNTGGMGNYTNTGGAARAARATHTGGGCNGTNCCNWSNCCNGARMGNTTYTTYATGCCNYTNTAYAARG
GNTGYWSNGGNGAYTTYAARAARTGGGTNGGNGCNCCNTTYACNGGNWSNWSNYTNGARYTNGGNCCNTGGWSNCCN
GARGTNCCNWSNACNYTNGARGTNTAYWSNTGYCAYCCNCCNMGNWSNCCNGCNAARMGNYTNCARYTNACNGARYT
NCARGARCCNGCNGARYTNGTNGARWSNGAYGGNGTNCCNAARCCNWSNTTYTGGCCNACNGCNCARAAYWSNGGNG
GNWSNGCNTAYWSNGARGARMGNGAYMGNCCNTAYGGNYTNGTNWSNATHGAYACNGTNACNGTNYTNGAYGCNGAR
GGNCCNTGYACNTGGCCNTGYWSNTGYGARGAYGAYGGNTAYCCNGCNYTNGAYYTNGAYGCNGGNYTNGARCCNWS
NCCNGGNYTNGARGAYCCNYTNYTNGAYGCNGGNACNACNGTNYTNWSNTGYGGNTGYGTNWSNGCNGGNWSNCCNG
GNYTNGGNGGNCCNYTNGGNWSNYTNYTNGAYMGNYTNAARCCNCCNYTNGCNGAYGGNGARGAYTGGGCNGGNGGN
YTNCCNTGGGGNGGNMGNWSNCCNGGNGGNGTNWSNGARWSNGARGCNGGNWSNCCNYTNGCNGGNYTNGAYATGGA
YACNTTYGAYWSNGGNTTYGTNGGNWSNGAYTGYWSNWSNCCNGTNGARTGYGAYTTYACNWSNCCNGGNGAYGARG
GNCCNCCNMGNWSNTAYYTNMGNCARTGGGTNGTNATHCCNCCNCCNYTNWSNWSNCCNGGNCCNCARGCNWSN

Nucleic acid sequence comparison of two DCRS3 embodiments:

```
DCRS3.2    1 ATGCCGCGTGGCTGGGCCGCCCCCTTGCTCCTGCTGCTGCTCCAGGGAGC    50
DCRS3.1    1 ATGCCGCGTGGCTGGGCCGCCCCCTTGCTCCTGCTGCTGCTCCAGGGA--    49
             ************************************************

DCRS3.2   51 CCTCGAGGGGATGGAGAGGAAGCTCTGCAGTCCCAAGCCACCCCCCACCA   100
DCRS3.1   49 --------------------------------------------------    49
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```
DCRS3.2  101 AGGCCTCTCTCCCCACTGACCCTCCAGGCTGGGGCTGCCCCGACCTCGTC 150
DCRS3.1   50 ---------------------------GCTGGGGCTGCCCCGACCTCGTC  72
                                        ***********************

DCRS3.2  151 TGCTACACCGATTACCTCCAGACGGTCATCTGCATCCTGGAAATGTGGAA 200
DCRS3.1   73 TGCTACACCGATTACCTCCAGACGGTCATCTGCATCCTGGAAATGTGGAA 122
             **************************************************

DCRS3.2  201 CCTCCACCCCAGCACGCTCACCCTTACCTGGATACTTTCTAATAATACTG 250
DCRS3.1  123 CCTCCACCCCAGCACGCTCACCCTTACCTGG------------------- 153
             *******************************

DCRS3.2  251 GGTGCTATATCAAGGACAGAACACTGGACCTCAGGCAAGACCAGTATGAA 300
DCRS3.1  154 -----------------------------------CAAGACCAGTATGAA 168
                                                ***************

DCRS3.2  301 GAGCTGAAGGACGAGGCCACCTCCTGCAGCCTCCACAGGTCGGCCCACAA 350
DCRS3.1  169 GAGCTGAAGGACGAGGCCACCTCCTGCAGCCTCCACAGGTCGGCCCACAA 218
             **************************************************

DCRS3.2  351 TGCCACGCATGCCACCTACACCTGCCACATGGATGTATTCCACTTCATGG 400
DCRS3.1  219 TGCCACGCATGCCACCTACACCTGCCACATGGATGTATTCCACTTCATGG 268
             **************************************************

DCRS3.2  401 CCGACGACATTTTCAGTGTCAACATCACAGACCAGTCTGGCAACTACTCC 450
DCRS3.1  269 CCGACGACATTTTCAGTGTCAACATCACAGACCAGTCTGGCAACTACTCC 318
             **************************************************

DCRS3.2  451 CAGGAGTGTGGCAGCTTTCTCCTGGCTGAGAGCA---------------- 484
DCRS3.1  319 CAGGANTGTGGCAGCTTTCTCCTGGCTGAGAGCATCAAGCCGGCTCCCCC 368
             ***** ****************************

DCRS3.2  485 --------------------------GACAGTATAATATCTCCTGGCGCT 508
DCRS3.1  369 TTTCAACGTGACTGTGACCTTCTCAGGACAGTATAATATNTCCTGGCGCT 418
                                       ************* **********

DCRS3.2  509 CAGATTACGAAGACCCTGCCTTCTACATGCTGAAGGGCAAGCTTCAGTAT 558
DCRS3.1  419 CAGATTACGAAGACCCTGCCTTCTACATGCTGAAAGGCAAGCTTCAATAT 468
             ********************************** *********** ***

DCRS3.2  559 GAGCTGCAGTACAGGAACCGGGGAGACCCCTGGGCTGTGAGTCCGAGGAG 608
DCRS3.1  469 GAGCTGCAGTACAGGAACCGGGGAGACCCCTGGGCTGTGAGTCCGAGGAG 518
             **************************************************

DCRS3.2  609 AAAGCTGATCTCAGTGGACTCAAGAAGTGTCTCCCTCCTCCCCCTGGAGT 658
DCRS3.1  519 AAAGCTGATCTCAGTGGACTCAAGAAGTGTCTCCCTCCTCCCCCTGGAGT 568
             **************************************************

DCRS3.2  659 TCCGCAAAGACTCGAGCTATGAGCTGCAGGTGCGGCAGGGCCCATGCCT 708
DCRS3.1  569 TCCGCAAAGACTCGAGCTATGAGCTGCANGTGCGGCAGGGCCCATGCCT 618
             **************************** *********************

DCRS3.2  709 GGCTCCTCCTACCAGGGGACCTGGAGTGAATGGAGTGACCCGGTCATCTT 758
DCRS3.1  619 GGCTCCTCCTACCAGGGGACCTGGAGTGAATGGAGTGACCCGGTCATCTG 668
             *************************************************
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```
DCRS3.2    759 TCAGACCCAGTCAGAGGAGTTAAAGGAAGGCTGGAACCCTCACCTGCTGC  808
DCRS3.1    669 TCAGACCCAGTCAGAGGAGTTAAAGGAAGGCTGGAACCCTCACCTGCTGC  718
               **************************************************

DCRS3.2    809 TTCTCCTCCTGCTTGTCATAGTCTTCATTCCTGCCTTCTGGAGCCTGAAG  858
DCRS3.1    719 TTCTCCTCCTGCTTGTCATAGTCTTCATTCCTGCCTTCTGGAGCCTGAAG  768
               **************************************************

DCRS3.2    859 ACCCATCCATTGTGGAGGCTATGGAAGAAGATATGGGCCGTCCCCAGCCC  908
DCRS3.1    769 ACCCATCCATTGTGGAGGCTATGGAAGAAGATATGGGCCGTCCCCAGCCC  818
               **************************************************

DCRS3.2    909 TGAGCGGTTCTTCATGCCCCTGTACAAGGGCTGCAGCGGAGACTTCAAGA  958
DCRS3.1    819 TGAGCGGTTCTTCATGCCCCTGTACAAGGGCTGCAGCGGAGACTTCAAGA  868
               **************************************************

DCRS3.2    959 AATGGGTGGGTGCACCCTTCACTGGCTCCAGCCTGGAGCTGGGACCCTGG 1008
DCRS3.1    869 AATGGGTGGGTGCACCCTTCACTGGCTCCAGCCTGGAGCTGGGACCCTGG  918
               **************************************************

DCRS3.2   1009 AGCCCAGAGGTGCCCTCCACCCTGGAGGTGTACAGCTGCCACCCACCACG 1058
DCRS3.1    919 AGCCCAGAGGTGCCCTCCACCCTGGAGGTGTACAGCTGCCACCCACCACG  968
               **************************************************

DCRS3.2   1059 GAGCCCGGCCAAGAGGCTGCAGCTCACGGAGCTACAAGAACCAGCAGAGC 1108
DCRS3.1    969 GAGCCCGGCCAAGAGGCTGCAGCTCACGGAGCTACAAGAACCAGCAGAGC 1018
               **************************************************

DCRS3.2   1109 TGGTGGAGTCTGACGGTGTGCCCAAGCCCAGCTTCTGGCCGACAGCCCAG 1158
DCRS3.1   1019 TGGTGGAGTCTGACGGTGTGCCCAAGCCCAGCTTCTGGCCGACAGCCCAG 1068
               **************************************************

DCRS3.2   1159 AACTCGGGGGGCTCAGCTTACAGTGAGGAGAGGGATCGGCCATACGGCCT 1208
DCRS3.1   1069 AACTCGGGGGGCTCAGCTTACAGTGAGGAGAGGGATCGGCCATACGGCCT 1118
               **************************************************

DCRS3.2   1209 GGTGTCCATTGACACAGTGACTGTGCTAGATGCAGAGGGGCCATGCACCT 1258
DCRS3.1   1119 GGTGTCCATTGACACAGTGACTGTGCTAGATGCAGAGGGGCCATGCACCT 1168
               **************************************************

DCRS3.2   1259 GGCCCTGCAGCTGTGAGGATGACGGCTACCCAGCCCTGGACCTGGATGCT 1308
DCRS3.1   1169 GGCCCTGCAGCTGTGAGGATGACGGCTACCCAGCCCTGGACCTGGATGCT 1218
               **************************************************

DCRS3.2   1309 GGCCTGGAGCCCAGCCCAGGCCTAGAGGACCCACTCTTGGATGCAGGGAC 1358
DCRS3.1   1219 GGCCTGGAGCCCAGCCCAGGCCTAGAGGACCCACTCTTGGATGCAGGGAC 1268
               **************************************************

DCRS3.2   1359 CACAGTCCTGTCCTGTGGCTGTGTCTCAGCTGGCAGCCCTGGGCTAGGAG 1408
DCRS3.1   1269 CACAGTCCTGTCCTGTGGCTGTGTCTCAGCTGGCAGCCCTGGGCTAGGAG 1318
               **************************************************

DCRS3.2   1409 GGCCCCTGGGAAGCCTCCTGGACAGACTAAAGCCACCCCTTGCAGATGGG 1458
DCRS3.1   1319 GGCCCCTGGGAAGCCTCCTGGACAGACTAAAGCCACCCCTTGCAGATGGG 1368
               **************************************************
```

```
DCRS3.2   1459 GAGGACTGGGCTGGGGGACTGCCCTGGGGTGGCCGGTCACCTGGAGGGGT 1508
DCRS3.1   1369 GAGGACTGGGCTGGGGGACTGCCCTGGGGTGGCCGGTCACCTGGAGGGGT 1418
               **************************************************

DCRS3.2   1509 CTCAGAGAGTGAGGCGGGCTCACCCCTGGCCGGCCTGGATATGGACACGT 1558
DCRS3.1   1419 CTCAGAGAGTGAGGCGGGCTCACCCCTGGCCGGCCTGGATATGGACACGT 1468
               **************************************************

DCRS3.2   1559 TTGACAGTGGCTTTGTGGGCTCTGACTGCAGCAGCCCTGTGGAGTGTGAC 1608
DCRS3.1   1469 TTGACAGTGGCTTTGTGGGCTCTGACTGCAGCAGCCCTGTGGAGTGTGAC 1518
               **************************************************

DCRS3.2   1609 TTCACCAGCCCCGGGGACGAAGGACCCCCCCGGAGCTACCTCCGCCAGTG 1658
DCRS3.1   1519 TTCACCAGCCCCGGGGACGAAGGACCCCCCCGGAGCTACCTCCGCCAGTG 1568
               **************************************************

DCRS3.2   1659 GGTGGTCATTCCTCCGCCACTTTCGAGCCCTGGACCCCAGGCCAGCTAA 1707
DCRS3.1   1569 GGTGGTCATTCCTCCGCCACTTTCGAGCCCTGGACCCCAGGCCAGCTAA 1617
               *************************************************
```

Table 3: Nucleotide and polypeptide sequences of DNAX Cytokine Receptor Subunit like embodiment 4 (DCRS4.1; cytor). Primate, e.g., human embodiment (see SEQ ID NO: 4 and 5). Predicted signal sequence indicated, but may vary by a few positions and depending upon cell type.

```
atg atg cct aaa cat tgc ttt cta ggc ttc ctc atc agt ttc ttc ctt    48
Met Met Pro Lys His Cys Phe Leu Gly Phe Leu Ile Ser Phe Phe Leu
    -20                 -15                 -10

act ggt gta gca gga act cag tca acg cat gag tct ctg aag cct cag    96
Thr Gly Val Ala Gly Thr Gln Ser Thr His Glu Ser Leu Lys Pro Gln
 -5                 -1   1               5                  10

agg gta caa ttt cag tcc cga aat ttt cac aac att ttg caa tgg cag   144
Arg Val Gln Phe Gln Ser Arg Asn Phe His Asn Ile Leu Gln Trp Gln
             15                  20                  25

cct ggg agg gca ctt act ggc aac agc agt gtc tat ttt gtg cag tac   192
Pro Gly Arg Ala Leu Thr Gly Asn Ser Ser Val Tyr Phe Val Gln Tyr
         30                  35                  40

aaa ata tat gga cag aga caa tgg aaa aat aaa gaa gac tgt tgg ggt   240
Lys Ile Tyr Gly Gln Arg Gln Trp Lys Asn Lys Glu Asp Cys Trp Gly
     45                  50                  55

act caa gaa ctc tct tgt gac ctt acc agt gaa acc tca gac ata cag   288
Thr Gln Glu Leu Ser Cys Asp Leu Thr Ser Glu Thr Ser Asp Ile Gln
 60                  65                  70                  75

gaa cct tat tac ggg agg agg ggc aaa aat aaa aat aaa ggg aat cct   336
Glu Pro Tyr Tyr Gly Arg Arg Gly Lys Asn Lys Asn Lys Gly Asn Pro
                 80                  85                  90

tgg ggg cca aaa caa agt aaa cgg aaa tca aag ggg aac cag aag acc   384
Trp Gly Pro Lys Gln Ser Lys Arg Lys Ser Lys Gly Asn Gln Lys Thr
             95                 100                 105
```

```
aac aca gtg act gcc cca gct gcc ctg aag gca ttt gct gga tgt gca   432
Asn Thr Val Thr Ala Pro Ala Ala Leu Lys Ala Phe Ala Gly Cys Ala
        110                 115                 120

aaa ata gat cct cca gtc atg aat ata acc caa gtc aat ggc tct ttg   480
Lys Ile Asp Pro Pro Val Met Asn Ile Thr Gln Val Asn Gly Ser Leu
    125                 130                 135

ttg gta att ctc cat gct cca aat tta cca tat aga tac caa aag gaa   528
Leu Val Ile Leu His Ala Pro Asn Leu Pro Tyr Arg Tyr Gln Lys Glu
140                 145                 150                 155

aaa aat gta tct ata gaa gat tac tat gaa cta cta tac cga gtt ttt   576
Lys Asn Val Ser Ile Glu Asp Tyr Tyr Glu Leu Leu Tyr Arg Val Phe
                160                 165                 170

ata att aac aat tca cta gaa aag gag caa aag gtt tat gaa ggg gct   624
Ile Ile Asn Asn Ser Leu Glu Lys Glu Gln Lys Val Tyr Glu Gly Ala
            175                 180                 185

cac aga gcg gtt gaa att gaa gct cta aca cca cac tcc agc tac tgt   672
His Arg Ala Val Glu Ile Glu Ala Leu Thr Pro His Ser Ser Tyr Cys
        190                 195                 200

gta gtg gct gaa ata tat cag ccc atg tta gac aga aga agt cag aga   720
Val Val Ala Glu Ile Tyr Gln Pro Met Leu Asp Arg Arg Ser Gln Arg
    205                 210                 215

agt gaa gag aga tgt gtg gaa att cca tga                           750
Ser Glu Glu Arg Cys Val Glu Ile Pro
220                 225
```

MMPKHCFLGFLISFFLTGVAGTQSTHESLKPQRVQFQSRNFHNILQWQPGRALTGNSSVYFVQYKIYGQRQWKNKED
CWGTQELSCDLTSETSDIQEPYYGRRGKNKNKGNPWGPKQSKRKSKGNQKTNTVTAPAALKAFAGCAKIDPPVMNIT
QVNGSLLVILHAPNLPYRYQKEKNVSIEDYYELLYRVFIINNSLEKEQKVYEGAHRAVEIEALTPHSSYCVVAEIYQ
PMLDRRSQRSEERCVEIP.

Nucleotide and polypeptide sequences of DNAX Cytokine Receptor Subunit like embodiments (DCRS4.2, cytorX700; SEQ ID NO: 27 and 28):

ATGATGCCTAAACATTGCTTTCTAGGCTTCCTCATCAGTTTCTTCCTTACTGGTGTAGCAGGAACTCAGTCAACGCA
TGAGTCTCTGAAGCCTCAGAGGGTACAATTTCAGTCCCGAAATTTTCACAACATTTTGCAATGGCAGCCCGGGAGGG
CACTTACTGGCAACAGCAGTGTCTATTTTGTGCAGTACAAAATATATGGACAGAGACAATGGAAAAATAAAGAAGAC
TGTTGGGGTACTCAAGAACTCTCTTGTGACCTTACCAGTGAAACCTCAGACATACAGGAACCTTATTACGGGAGGGT
GAGGGCGGCCTCGGCTGGGAGCTACTCAGAATGGAGCATGACGCCGCGGTTCACTCCCTGGTGGGAAACAAAAATAG
ATCCTCCAGTCATGAATATAACCCAAGTCAATGGCTCTTTGTTGGTAATTCTCCATGCTCCAAATTTACCATATAGA
TACCAAAAGGAAAAAAATGTATCTATAGAAGATTACTATGAACTACTATACCGAGTTTTTATAATTAACAATTCACT
AGAAAAGGAGCAAAAGGTTTATGAAGGGGCTCACAGAGCGGTTGAAATTGAAGCTCTAACACCACACTCCAGCTACT
GTGTAGTGGCTGAAATATATCAGCCCATGTTAGACAGAAGAAGTCAGAGAAGTGAAGAGAGATGTGTGGAAATTCCA
TGA

```
atg atg cct aaa cat tgc ttt cta ggc ttc ctc atc agt ttc ttc ctt   48
Met Met Pro Lys His Cys Phe Leu Gly Phe Leu Ile Ser Phe Phe Leu
    -20                 -15                 -10

act ggt gta gca gga act cag tca acg cat gag tct ctg aag cct cag   96
Thr Gly Val Ala Gly Thr Gln Ser Thr His Glu Ser Leu Lys Pro Gln
-5                  -1   1                   5                  10
```

agg gta caa ttt cag tcc cga aat ttt cac aac att ttg caa tgg cag 144
Arg Val Gln Phe Gln Ser Arg Asn Phe His Asn Ile Leu Gln Trp Gln
15 20 25

ccc ggg agg gca ctt act ggc aac agc agt gtc tat ttt gtg cag tac 192
Pro Gly Arg Ala Leu Thr Gly Asn Ser Ser Val Tyr Phe Val Gln Tyr
30 35 40

aaa ata tat gga cag aga caa tgg aaa aat aaa gaa gac tgt tgg ggt 240
Lys Ile Tyr Gly Gln Arg Gln Trp Lys Asn Lys Glu Asp Cys Trp Gly
45 50 55

act caa gaa ctc tct tgt gac ctt acc agt gaa acc tca gac ata cag 288
Thr Gln Glu Leu Ser Cys Asp Leu Thr Ser Glu Thr Ser Asp Ile Gln
60 65 70 75

gaa cct tat tac ggg agg gtg agg gcg gcc tcg gct ggg agc tac tca 336
Glu Pro Tyr Tyr Gly Arg Val Arg Ala Ala Ser Ala Gly Ser Tyr Ser
80 85 90

gaa tgg agc atg acg ccg cgg ttc act ccc tgg tgg gaa aca aaa ata 384
Glu Trp Ser Met Thr Pro Arg Phe Thr Pro Trp Trp Glu Thr Lys Ile
95 100 105

gat cct cca gtc atg aat ata acc caa gtc aat ggc tct ttg ttg gta 432
Asp Pro Pro Val Met Asn Ile Thr Gln Val Asn Gly Ser Leu Leu Val
110 115 120

att ctc cat gct cca aat tta cca tat aga tac caa aag gaa aaa aat 480
Ile Leu His Ala Pro Asn Leu Pro Tyr Arg Tyr Gln Lys Glu Lys Asn
125 130 135

gta tct ata gaa gat tac tat gaa cta cta tac cga gtt ttt ata att 528
Val Ser Ile Glu Asp Tyr Tyr Glu Leu Leu Tyr Arg Val Phe Ile Ile
140 145 150 155

aac aat tca cta gaa aag gag caa aag gtt tat gaa ggg gct cac aga 576
Asn Asn Ser Leu Glu Lys Glu Gln Lys Val Tyr Glu Gly Ala His Arg
160 165 170

gcg gtt gaa att gaa gct cta aca cca cac tcc agc tac tgt gta gtg 624
Ala Val Glu Ile Glu Ala Leu Thr Pro His Ser Ser Tyr Cys Val Val
175 180 185

gct gaa ata tat cag ccc atg tta gac aga aga agt cag aga agt gaa 672
Ala Glu Ile Tyr Gln Pro Met Leu Asp Arg Arg Ser Gln Arg Ser Glu
190 195 200

gag aga tgt gtg gaa att cca tga 696
Glu Arg Cys Val Glu Ile Pro
205 210

>cytorX700
MMPKHCFLGFLISFFLTGVAGTQSTHESLKPQRVQFQSRNFHNILQWQPGRALTGNSSVYFVQYKIYGQRQWKNKED
CWGTQELSCDLTSETSDIQEPYYGRVRAASAGSYSEWSMTPRFTPWWETKIDPPVMNITQVNGSLLVILHAPNLPYR
YQKEKNVSIEDYYELLYRVFIINNSLEKEQKVYEGAHRAVEIEALTPHSSYCVVAEIYQPMLDRRSQRSEERCVEIP

Nucleotide and polypeptide sequences of DNAX Cytokine Receptor Subunit like embodiments (DCRS4.3 cytorX600; SEQ ID NO: 30 and 31):

```
ATGATGCCTAAACATTGCTTTCTAGGCTTCCTCATCAGTTTTTCCTTACTGGTGTAGCAGGAACTCAGTCAACGCA
TGAGTCTCTGAAGCCTCAGAGGGTACAATTTCAGTCCCGAAATTTTCACAACATTTTGCAATGGCAGCCTGGGAGGG
CACTTACTGGCAACAGCAGTGTCTATTTTGTGCAGTACAAAATATATGGACAGAGACAATGGAAAAATAAAGAAGAC
TGTTGGGGTACTCAAGAACTCTCTTGTGACCTTACCAGTGAAACCTCAGACATACAGGAATCTTATTACGGGAGGGT
GAGGGCGGCCTCGGCTGGGAGCTACTCAGAATGGAGCATGACGCCGCGGTTCACTCCCTGGTGGGAAAGAGCAAAAG
GTTTATGAAGGGGCTCACAGAGCGGTTGAAATTGAAGCTCTAACACCACACTCCAGCTACTGTGTAGTGGCTGAAAT
ATATCAGCCCACGTTAGACAGAAGAAGTCAGAGAAGTGAAGAGAGATGTGTGGAAATTCCATGA
```

```
atg atg cct aaa cat tgc ttt cta ggc ttc ctc atc agt ttt ttc ctt    48
Met Met Pro Lys His Cys Phe Leu Gly Phe Leu Ile Ser Phe Phe Leu
    -20                 -15                 -10

act ggt gta gca gga act cag tca acg cat gag tct ctg aag cct cag    96
Thr Gly Val Ala Gly Thr Gln Ser Thr His Glu Ser Leu Lys Pro Gln
 -5                 -1   1               5                  10

agg gta caa ttt cag tcc cga aat ttt cac aac att ttg caa tgg cag    144
Arg Val Gln Phe Gln Ser Arg Asn Phe His Asn Ile Leu Gln Trp Gln
            15                  20                  25

cct ggg agg gca ctt act ggc aac agc agt gtc tat ttt gtg cag tac    192
Pro Gly Arg Ala Leu Thr Gly Asn Ser Ser Val Tyr Phe Val Gln Tyr
        30                  35                  40

aaa ata tat gga cag aga caa tgg aaa aat aaa gaa gac tgt tgg ggt    240
Lys Ile Tyr Gly Gln Arg Gln Trp Lys Asn Lys Glu Asp Cys Trp Gly
    45                  50                  55

act caa gaa ctc tct tgt gac ctt acc agt gaa acc tca gac ata cag    288
Thr Gln Glu Leu Ser Cys Asp Leu Thr Ser Glu Thr Ser Asp Ile Gln
60                  65                  70                  75

gaa tct tat tac ggg agg gtg agg gcg gcc tcg gct ggg agc tac tca    336
Glu Ser Tyr Tyr Gly Arg Val Arg Ala Ala Ser Ala Gly Ser Tyr Ser
                80                  85                  90

gaa tgg agc atg acg ccg cgg ttc act ccc tgg tgg gaa aga gca aaa    384
Glu Trp Ser Met Thr Pro Arg Phe Thr Pro Trp Trp Glu Arg Ala Lys
            95                 100                 105

ggt tta tgaaggggct cacagagcgg ttgaaattga agctctaaca ccacactcca    440
Gly Leu

gctactgtgt agtggctgaa atatatcagc ccacgttaga cagaagaagt cagagaagtg 500

aagagagatg tgtggaaatt ccatga                                      526
```

>cytorX600
MMPKHCFLGFLISFFLTGVAGTQSTHESLKPQRVQFQSRNFHNILQWQPGRALTGNSSVYFVQYKIYGQRQWKNKED
CWGTQELSCDLTSETSDIQESYYGRVRAASAGSYSEWSMTPRFTPWWERAKGL.

Polypeptide sequence comparison of DCRS4.1, DCRS4.2 and DCRS4.3:

```
DCRS4.1     1 MMPKHCFLGFLISFFLTGVAGTQSTHESLKPQRVQFQSRNFHNILQWQPG  50
DCRS4.2     1 MMPKHCFLGFLISFFLTGVAGTQSTHESLKPQRVQFQSRNFHNILQWQPG  50
DCRS4.3     1 MMPKHCFLGFLISFFLTGVAGTQSTHESLKPQRVQFQSRNFHNILQWQPG  50
              **************************************************

DCRS4.1    51 RALTGNSSVYFVQYKIYGQRQWKNKEDCWGTQELSCDLTSETSDIQEPYY 100
DCRS4.2    51 RALTGNSSVYFVQYKIYGQRQWKNKEDCWGTQELSCDLTSETSDIQEPYY 100
DCRS4.3    51 RALTGNSSVYFVQYKIYGQRQWKNKEDCWGTQELSCDLTSETSDIQESYY 100
              *********************************************** **

DCRS4.1   101 GR-RGKNKNKGNPWGPKQSKRKSKGNQKTNTVTAPAALKAFAGCAKIDPP 149
DCRS4.2   101 GRVRAASAGSYSEWS--MTPRFTP-----------------WWETKIDPP 131
DCRS4.3   101 GRVRAASAGSYSEWS--MTPRFTP-----------------WWE------ 119
              ** *     .    *     . * .

DCRS4.1   150 VMNITQVNGSLLVILHAPNLPYRYQKEKNVSIEDYYELLYRVFIINNSLE 199
DCRS4.2   132 VMNITQVNGSLLVILHAPNLPYRYQKEKNVSIEDYYELLYRVFIINNSLE 181
DCRS4.3   123 -------------------------RAKGL                     130
                                       .. *..

DCRS4.1   200 KEQKVYEGAHRAVEIEALTPHSSYCVVAEIYQPMLDRRSQRSEERCVEIP 249
DCRS4.2   182 KEQKVYEGAHRAVEIEALTPHSSYCVVAEIYQPMLDRRSQRSEERCVEIP 231
DCRS4.3   131                                                    130
```

Table 4: Reverse Translation of primate, e.g., human, DCRS4.1 (SEQ ID NO: 6). N may be A, C, G, or T.

ATGATGCCNAARCAYTGYTTYYTNGGNTTYYTNATHWSNTTYTTYYTNACNGGNGTNGCNGGNACNCARWSNACNCA
YGARWSNYTNAARCCNCARMGNGTNCARTTYCARWSNMGNAAYTTYCAYAAYATHYTNCARTGGCARCCNGGNMGNG
CNYTNACNGGNAAYWSNWSNGTNTAYTTYGTNCARTAYAARATHTAYGGNCARMGNCARTGGAARAAYAARGARGAY
TGYTGGGGNACNCARGARYTNWSNTGYGAYYTNACNWSNGARACNWSNGAYATHCARGARCCNTAYTAYGGNMGNMG
NGGNAARAAYAARAAYAARGGNAAYCCNTGGGGNCCNAARCARWSNAARMGNAARWSNAARGGNAAYCARAARACNA
AYACNGTNACNGCNCCNGCNGCNYTNAARGCNTTYGCNGGNTGYGCNAARATHGAYCCNCCNGTNATGAAYATHACN
CARGTNAAYGGNWSNYTNYTNGTNATHYTNCAYGCNCCNAAYYTNCCNTAYMGNTAYCARAARGARAARAAYGTNWS
NATHGARGAYTAYTAYGARYTNYTNTAYMGNGTNTTYATHATHAAYAAYWSNYTNGARAARGARCARAARGTNTAYG
ARGGNGCNCAYMGNGCNGTNGARATHGARGCNYTNACNCCNCAYWSNWSNTAYTGYGTNGTNGCNGARATHTAYCAR
CCNATGYTNGAYMGNMGNWSNCARMGNWSNGARGARMGNTGYGTNGARATHCCN

Reverse Translation of primate, e.g., human, DCRS4.2 (SEQ ID NO: 29). N may be A, C, G, or T.

ATGATGCCNAARCAYTGYTTYYTNGGNTTYYTNATHWSNTTYTTYYTNACNGGNGTNGCNGGNACNCARWSNACNCA
YGARWSNYTNAARCCNCARMGNGTNCARTTYCARWSNMGNAAYTTYCAYAAYATHYTNCARTGGCARCCNGGNMGNG
CNYTNACNGGNAAYWSNWSNGTNTAYTTYGTNCARTAYAARATHTAYGGNCARMGNCARTGGAARAAYAARGARGAY
TGYTGGGGNACNCARGARYTNWSNTGYGAYYTNACNWSNGARACNWSNGAYATHCARGARCCNTAYTAYGGNMGNGT
NMGNGCNGCNWSNGCNGGNWSNTAYWSNGARTGGWSNATGACNCCNMGNTTYACNCCNTGGTGGGARACNAARATHG
AYCCNCCNGTNATGAAYATHACNCARGTNAAYGGNWSNYTNYTNGTNATHYTNCAYGCNCCNAAYYTNCCNTAYMGN
TAYCARAARGARAARAAYGTNWSNATHGARGAYTAYTAYGARYTNYTNTAYMGNGTNTTYATHATHAAYAAYWSNYT
NGARAARGARCARAARGTNTAYGARGGNGCNCAYMGNGCNGTNGARATHGARGCNYTNACNCCNCAYWSNWSNTAYT
GYGTNGTNGCNGARATHTAYCARCCNATGYTNGAYMGNMGNWSNCARMGNWSNGARGARMGNTGYGTNGARATHCCN

Reverse Translation of primate, e.g., human, DCRS4.3 (SEQ ID NO: 32). N may be A, C, G, or T.

ATGATGCCNAARCAYTGYTTYYTNGGNTTYYTNATHWSNTTYTTYYTNACNGGNGTNGCNGGNACNCARWSNACNCA
YGARWSNYTNAARCCNCARMGNGTNCARTTYCARWSNMGNAAYTTYCAYAAYATHYTNCARTGGCARCCNGGNMGNG
CNYTNACNGGNAAYWSNWSNGTNTAYTTYGTNCARTAYAARATHTAYGGNCARMGNCARTGGAARAAYAARGARGAY

TGYTGGGGNACNCARGARYTNWSNTGYGAYYTNACNWSNGARACNWSNGAYATHCARGARWSNTAYTAYGGNMGNGTNMGNGCNGCNWSNGCNGGNWSNTAYWSNGARTGGWSNATGACNCCNMGNTTYACNCCNTGGTGGGARMGNGCNAARGGNYTN

Nucleic acid sequence comparison of three DCRS4 embodiments:

```
DCRS4.1    1 ATGATGCCTAAACATTGCTTTCTAGGCTTCCTCATCAGTTTCTTCCTTAC  50
DCRS4.2    1 ATGATGCCTAAACATTGCTTTCTAGGCTTCCTCATCAGTTTCTTCCTTAC  50
DCRS4.3    1 ATGATGCCTAAACATTGCTTTCTAGGCTTCCTCATCAGTTTTTTCCTTAC  50
             ***************************************** ********

DCRS4.1   51 TGGTGTAGCAGGAACTCAGTCAACGCATGAGTCTCTGAAGCCTCAGAGGG 100
DCRS4.2   51 TGGTGTAGCAGGAACTCAGTCAACGCATGAGTCTCTGAAGCCTCAGAGGG 100
DCRS4.3   51 TGGTGTAGCAGGAACTCAGTCAACGCATGAGTCTCTGAAGCCTCAGAGGG 100
             **************************************************

DCRS4.1  101 TACAATTTCAGTCCCGAAATTTTCACAACATTTTGCAATGGCAGCCTGGG 150
DCRS4.2  101 TACAATTTCAGTCCCGAAATTTTCACAACATTTTGCAATGGCAGCCCGGG 150
DCRS4.3  101 TACAATTTCAGTCCCGAAATTTTCACAACATTTTGCAATGGCAGCCTGGG 150
             ********************************************** ***

DCRS4.1  151 AGGGCACTTACTGGCAACAGCAGTGTCTATTTTGTGCAGTACAAAATATA 200
DCRS4.2  151 AGGGCACTTACTGGCAACAGCAGTGTCTATTTTGTGCAGTACAAAATATA 200
DCRS4.3  151 AGGGCACTTACTGGCAACAGCAGTGTCTATTTTGTGCAGTACAAAATATA 200
             **************************************************

DCRS4.1  201 TGGACAGAGACAATGGAAAAATAAAGAAGACTGTTGGGGTACTCAAGAAC 250
DCRS4.2  201 TGGACAGAGACAATGGAAAAATAAAGAAGACTGTTGGGGTACTCAAGAAC 250
DCRS4.3  201 TGGACAGAGACAATGGAAAAATAAAGAAGACTGTTGGGGTACTCAAGAAC 250
             **************************************************

DCRS4.1  251 TCTCTTGTGACCTTACCAGTGAAACCTCAGACATACAGGAACCTTATTAC 300
DCRS4.2  251 TCTCTTGTGACCTTACCAGTGAAACCTCAGACATACAGGAACCTTATTAC 300
DCRS4.3  251 TCTCTTGTGACCTTACCAGTGAAACCTCAGACATACAGGAATCTTATTAC 300
             ***************************************** ********

DCRS4.1  301 GGGAGGAGGGGCAAAAATAAAAATAAAGGGAATCCTTGGGGGCCAAAACA 350
DCRS4.2  301 GGGAGGGTG-----------------AGGGCGGCCTCGGC---------- 323
DCRS4.3  301 GGGAGGGTG-----------------AGGGCGGCCTCGGC---------- 323
             ******  *                 ****   *** **

DCRS4.1  351 AAGTAAACGGAAATCAAAGGGGAACCAGAAGACCAACACAGTGACTGCCC 400
DCRS4.2  324 ---TGGGAGCTACTCAGAATGGAGCATGA-------CGCCGCGGTTCACT 363
DCRS4.3  324 ---TGGGAGCTACTCAGAATGGAGCATGA-------CGCCGCGGTTCACT 363
                *    *  * *** *  *** *  **       * * * *  *  *

DCRS4.1  401 CAGCTGCCCTGAAGGCATTTGCTGGATGTGCAAAAATAGATCCTCCAGTC 450
DCRS4.2  364 C------CCTGGTGGGAA-----------ACAAAAATAGATCCTCCAGTC 396
DCRS4.3  364 C------CCTGGTGGGAAAGAGCAAAAGGTTTATGAAGGGGCTCACAGA- 406
             *      ****  ** *               *  *  *  *   ***

DCRS4.1  451 ATGAATATAACCCAAGTC--AATGGCTCTTTGTTGGTAATTCTCCATGCT 498
DCRS4.2  397 ATGAATATAACCCAAGTC--AATGGCTCTTTGTTGGTAATTCTCCATGCT 444
DCRS4.3  407 GCGGTTGAAATTGAAGCTCTAACACCACACTCCAGCTACTGTGTAGTGGC 456
               *  *  **   ***    **   * *  *   * ** *      **
```

```
DCRS4.1   499 CCAAATTTACCATATAGATACCAAAAGGAAAAAAATGTATCTATAGAAGA 548
DCRS4.2   445 CCAAATTTACCATATAGATACCAAAAGGAAAAAAATGTATCTATAGAAGA 494
DCRS4.3   457 TGAAATATATCA-GCCCACGTTAGACAGAAGAAGTCAGAGAAGT-GAAGA 504
                **** ** **     *    * *  *** **     *    * *****

DCRS4.1   549 TTACTATGAACTACTATACCGAGTTTTTATAATTAACAATTCACTAGAAA 598
DCRS4.2   495 TTACTATGAACTACTATACCGAGTTTTTATAATTAACAATTCACTAGAAA 544
DCRS4.3   505 GAGATGTGTGGAAATTCCATGA                             526
                  * **    * *     **

DCRS4.1   599 AGGAGCAAAAGGTTTATGAAGGGGCTCACAGAGCGGTTGAAATTGAAGCT 648
DCRS4.2   545 AGGAGCAAAAGGTTTATGAAGGGGCTCACAGAGCGGTTGAAATTGAAGCT 594
DCRS4.3   527                                                    526

DCRS4.1   649 CTAACACCACACTCCAGCTACTGTGTAGTGGCTGAAATATATCAGCCCAT 698
DCRS4.2   595 CTAACACCACACTCCAGCTACTGTGTAGTGGCTGAAATATATCAGCCCAT 644
DCRS4.3   527                                                    526

DCRS4.1   699 GTTAGACAGAAGAAGTCAGAGAAGTGAAGAGAGATGTGTGGAAATTCCAT 748
DCRS4.2   645 GTTAGACAGAAGAAGTCAGAGAAGTGAAGAGAGATGTGTGGAAATTCCAT 694
DCRS4.3   527                                                    526

DCRS4.1   749 GA 750
DCRS4.2   695 GA 696
DCRS4.3   527    526
```

Table 5: Alignment of various cytokine receptor subunits with DCRS3.1. IL-2R is SEQ ID NO: 7; IL-9R is SEQ ID NO: 8; GM/IL-3/5 receptor b subunit common (ILRbc) is SEQ ID NO: 9; TPOR is SEQ ID NO: 10; and IL-7R is SEQ ID NO: 11 (see GenBank).

```
IL-2R_HU   VNG--TSQFTC---FYNSRANISCVWSQ-DGALQDTSCQVHAWPDRRRWN-------QTC
DCRS3_HU   LCS--PKPPPT----KASLPTDPPGWGC-PDLVCYTDYLQTVICILEMWN--LHP--STL
IL-9R_HU   ICI----C-TC-----VCLGVSVTGEGQGPRSRTFTCLTNNILRIDCHWS---APELGQG
ILRbc_HU   ILTPNGNEDTTADFFLTTMPTDSLSVST-LPLPEVQCFVFNVEYMNCTWNSSSEPQPTNL
TPOR_HU    LLASDSEPLKC---FSRTFEDLTCFWDE-EEAAPSGTYQLLYAYPREKPR--ACP--LSS
IL-7R_HU   VSGESGYAQNG---DLEDAELDDYSFSC-YSQLEVNGSQHSLTCAFEDPD--------VN
           :                         .

IL-2R_HU   ELLPVSQASWACN----------LILG---------APDS--QKLTTVD---------IV
DCRS3_HU   TLTWILSNNTGCYIKDR-----TLDLRQ-DQYE--ELKDEA-TSCSLHR-----SAHNAT
IL-9R_HU   SSPWLLFTSNQAPG----G-THKCILR--GSECTVVLPPE--AVLVPSD--------NFT
ILRbc_HU   TLHYWYKNSDNDK-------VQKCSHY--------LFSEEITSGCQLQK-K---EIHLYQ
TPOR_HU    QSMPHFGTRYVCQFPDQ--EEVRLFFPLHLWVKNVFLNQTRTQRVLFVDSVGLPAPPSII
IL-7R_HU   TTNLEFEICGALV------EVKCLNFR--------KLQEIYFIETKKFL---------LI

IL-2R_HU   TLRVLCREGVRWRV---MAIQDFKPFENLRLMAPISLQV----VHVETHRCNIS---WEI
DCRS3_HU   HATYTCHMDVFHF----MADDIFS--VNITDQSGNYSQECGSFLLAESRQYNIS---WRS
IL-9R_HU   ITFHHCMSGREQVS---LVDPEYLPRRHVKLDPPSDLQS-----NISSGHCILT---WSI
ILRbc_HU   TFVVQLQDPREPRR---QATQMLKLQNLVIPWAPENLTL----HKLSESQLELN---WNN
TPOR_HU    KAMGGSQPGELQISWEEPAPEISDFLRYELRYGPRDPKNS---TGPTVIQLIATETCCPA
IL-7R_HU   GKSNICVK-VGEKS---LTCKKIDLTTIVKPEAPFDLSVI---YREGANDFVVT---FNT
                             .                                  .
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```
IL-2R_HU     SQASHYFERHLE---FEARTLSPGHTWEEAPLLTLK-------QKQEWICLETLT-PDTQ
DCRS3_HU     DYEDPAFYMLKGKLQYELQYRNRGDPWAVSPRRKLIS-----VDSRSVSLLPLEFRKDSS
IL-9R_HU     SPALEPMTTLLS---YELAFKKQEEAWEQAQHRDHIV-----G-VTWLILEAFELDPGFI
ILRbc_HU     RFLNHCLEHLV-------QYRTD---WDHSWTEQSV------DYRHKFSLPSVDGQKRYT
TPOR_HU      LQRPHSASALD-----QSPCAQPTMPWQDGPKQTSPSREASALTAEGGSCLISGLQPGNS
IL-7R_HU     SHLQKKYVKVLMHD-VAYRQEKDENKWTHVNLSST---------KLTLLQRK--LQPAAM
                                          *

IL-2R_HU     YEFQVRVKPLQGEFT---------TWSPWSQPLAFRTKPAALG
DCRS3_HU     YELQVRAGPMPGSSYQG-------TWSEWSDPVIFQTQSEELK
IL-9R_HU     HEARLRVQMATLEDDVVEEERYTGQWSEWSQPVCFQAPQRQGP
ILRbc_HU     FRVRSRFNPLCGSAQ---------HWSEWSHPIHWGSNTSKEN
TPOR_HU      YWLQLRSEPDGISLGG--------SWGSWSLPVTVDLPGDAVA
IL-7R_HU     YEIKVRSIPDHYFKG---------FWSEWSPSYYFRTPEINNS
              .  : *                  *. ** .
```

Alignment of various cytokine receptor subunits with DCRS4.1. IL-10Rb is the beta subunit of IL-10R, human is SEQ ID NO: 12, mouse is SEQ ID NO: 13; INaR1 is the beta subunit of IFNa with human SEQ ID NO: 14 and mouse SEQ ID NO: 15; INgR is interferon gamma receptor subunit alpha with human SEQ ID NO: 16 and mouse SEQ ID NO: 17; IL-10Ra is the alpha receptor subunit with mouse SEQ ID NO: 18 and human SEQ ID NO: 19; INgS (SEQ ID NO: 20) is the beta receptor subunit for INFg; Zcytor7 (SEQ ID NO: 21) and CYTOR11 (SEQ ID NO: 22) are from patent filings from Zymogenetics, and INaR2 (SEQ ID NO: 23) is the beta subunit of the receptor for IFNa.

```
IL-10Rb_Hu     PENVRMNSVNFKNILQWES-PAFAKGNL--TFTAQYLSY---------RIFQDKCMNTTL
IL-10Rb_Mu     PEKVRMNSVNFKNILQWEV-PAFPKTNL--TFTAQYESY---------RSFQDHCKRTAS
INaR1_HU       PQKVEVDIIDDNFILRWNR-SDESVGNV--TFSFDYQKTGMD-----NWIKLSGCQNITS
INaR1_MU       PENIDVYIIDDNYTLKWSS-HGESMGSV--TFSAEYRTKDEA-----KWLKVPECQHTTT
INgR_HU        PTNVTIESYNMNPIVYWEY-QIMPQVP---VFTVEVKNYGVK-----NSEWIDACINISH
INgR_MU        PTNVLIKSYNLNPVVCWEY-QNMSQTP---IFTVQVKVY--------SGSWTDSCTNISD
IL-10Ra_Mu     PSYVWFEARFFQHILHWKP-IPNQSEST--YYEVALKQYGNS-----TWNDIHICRKAQA
IL-10Ra_Hu     PPSVWFEAEFFHHILHWTP-IPNQSEST--CYEVALLRYGIE-----SWNSISNC--SQT
INgS_HU        PLNPRLHLYNDEQILTWEP-SPSSNDPRPVVYQVEYSFIDGSW----HRLLEPNCTDITE
Zcytor7_Hu     PANITFLSINMKNVLQWTPPEGLQGVKV--TYTVQYFIYGQK-----KWLNKSECRNINR
CYTOR11_HU     LQHVKFQSSNFENILTWDS-GPEGTPDT--VYSIEYKTYGER-----DWVAKKGCQRITR
INaR2_HU       SCTFKISLRNFRSILSWEL-KNHSIVPTHYTLLYTIMSKPE------DLKVVKNCANTTR
DCRS4.1_HU     PQRVQFQSRNFHNILQWQPGRALTGNSS--VYFVQYKIYGQR-----QWKNKEDCWGTQE
                    .      .  : *                                  *

IL-10Rb_Hu     TECDFSSLSK------YGDHTLRVRAEFADEHSDWVNIT-FCPVDDTIIGPPG--MQVEV
IL-10Rb_Mu     TQCDFSHLSK------YGDYTVRVRAELADEHSEWVNVT-FCPVEDTIIGPPE--MQIES
INaR1_HU       TKCNFSSLKLN----VYEEIKLRIRAEKEN-TSSWYEVDSFTPFRKAQIGPPE--VHLEA
INaR1_MU       TKCEFSLLDTN----VYIKTQFRVRAEEGNSTSSWNEVDPFIPFYTAHMSPPE--VRLEA
INgR_HU        HYCNISDHVGDP----SNSLWVRVKARVGQKESAYAKSEEFAVCRDGKIGPPKLDIR-KE
INgR_MU        HCCNIYGQIMYP----DVSAWARVKAKVGQKESDYARSKEFLMCLKGKVGPPGLEIRRKK
IL-10Ra_Mu     LSCDLTTFTLDLYHR-SYGYRARVRAVDNSQYSNWTTTETRFTVDEVILTVDS--VTLKA
IL-10Ra_Hu     LSYDLTAVTLDLYH--SNGYRARVRAVDGSRHSNWTVTNTRFSVDEVTLTVGS--VNLEI
INgS_HU        TKCDLTGGGRLKLFPHPFTVFLRVRAKRGNLTSKWVGLEPFQHYENVTVGPPKN-ISVTP
Zcytor7_Hu     TYCDLSAETSDY----EHQYYAKVKAIWGTKCSKWAESGRFYPFLETQIGPPE--VALTT
CYTOR11_HU     KSCNLTVETGN----LTELYYARVTAVSAGGRSATKMTDRFSSLQHTTLKPPDV-TCISK
INaR2_HU       SFCDLTDEWRS-----THEAYVTVLEGFSGNTTLFSCSHNFWLAIDMSFEPPE--FEIVG
DCRS4.1_HU     LSCDLTSETSD-----IQEPYYGRRGKNKNKGNPWGPKQSKRKSKGNQKTNTVT-APAAL
                 ::
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IL-10Rb_Hu    LADSLHMRFLAPKIENEYE---TWTMKNVYNSWTYNVQYWKNGTDEKFQ-ITPQYDFEVL
IL-10Rb_Mu    LAESLHLRFSAPQIENEPE---TWTLKNIYDSWAYRVQYWKNGTNEKFQ-VVSPYDSEVL
INaR1_HU      EDKAIVIHISPGTKDSV-----MWALD--GLSFTYSLLIWKNSSGVEER-IENIYSRHKI
INaR1_MU      EDKAILVHISPPGQDGN-----MWALE--KPSFSYTIRIWQKSSSDKKT-INSTYYVEKI
INgR_HU       EKQIMIDIFHPSVFVNGDEQEVDYDPETTCYIRVYNVYVRMNGS-EIQY-KILTQKEDDC
INgR_MU       EEQLSVLVFHPEVVVNGESQGTMFGDGSTCYTFDYTVYVEHNRSGEILH-TKHTVEKEEC
IL-10Ra_Mu    MDGIIYGTIHPPRPTITPA--GDEYEQVFKDLRVYKISIRKFS--ELKN-ATKRVKQETF
IL-10Ra_Hu    HNGFILGKIQLPRPKMAPA--NDTYESIFSHFREYEIAIRKVPG-NFTF-THKKVKHENF
INgS_HU       GKGSLVIHFSPPFDVFHG------------ATFQYLVHYWEKSETQQEQ-VEGPFKSNSI
Zcytor7_Hu    DEKSISVVLTAPEKWKRNPEDLPVSMQQIYSNLKYNVSVLNTKSNRTWS-QCVTNHTLVL
CYTOR11_HU    VRSIQMIVHPTPTPIRAGDG-HRLTLEDIFHDLFYHLELQVNRTYQMHL-GGKQREYEFF
INaR2_HU      FTNHINVMVKFPSIVEEEL-------Q---FDLSLVIEEQSEGIVKKHKPEIKGNMSGNF
DCRS4.1_HU    KAFAGCAKIDPPVMNITQ------------VNGSLLVILHAPNLPYRYQ-KEKNVSIEDY
                                                  :

IL-10Rb_Hu    RN-----------------LEPWTTYCVQVRGFLPDRN----------KAGEWSEPVCEQ
IL-10Rb_Mu    RN-----------------LEPWTTYCIQVQGFLLDQN----------RTGEWSEPICER
INaR1_HU      YK-----------------LSPETTYCLKVKAALLTSW----------KIGVYSPVHCIK
INaR1_MU      PE-----------------LLPETTYCLEVKAIHPSLK----------KHSNYSTVQCIS
INgR_HU       DEIQCQLAI--------PVSSLNSQYCVSAEGVLHVWG----------VTTEKSKEVCIT
INgR_MU       NETLCELNI--------SVSTLDSRYCISVDGISSFWQ----------VRTEKSKDVCIP
IL-10Ra_Mu    TLT---------------VPIGVRKFCVKVLPRLESRI----------NKAEWSEEQCLL
IL-10Ra_Hu    SLL---------------TSGEVGEFCVQVKPSVASRS----------NKGMWSKEECIS
INgS_HU       VLG---------------NLKPYRVYCLQTEAQLILKNKK------IRPHGLLSNVSCHE
Zcytor7_Hu    TW-----------------LEPNTLYCVHVESFVPGPP----------RRAQPSEKQCAR
CYTOR11_HU    GLTPDTEFLGTIMICVPTWAKESAPYMCRVKTLPDRTWTYSFSGAFLFSMGFLVAVLCYL
INaR2_HU      TYIID-------------KLIPNTNYCVSVYLEHSDEQ-----------AVIKSPLKCTL
DCRS4.1_HU    YE-----------------------LLYRVFIINNSLE----------KEQKVYEGAHRA
                                           .

IL-10Rb_Hu    TTHDETVP-
IL-10Rb_Mu    TGNDEITP-
INaR1_HU      TTVENELPP
INaR1_MU      TTVANKMPV
INgR_HU       IFNSSIKG-
INgR_MU       PFHDDRKD-
IL-10Ra_Mu    ITTEQYFT-
IL-10Ra_Hu    LT-RQYFT-
INgS_HU       TTANASAR-
Zcytor7_Hu    TLKDQSSE-
CYTOR11_HU    SYRYVTKPP
INaR2_HU      LPPGQESES
DCRS4.1_HU    VEIEALTP-
```

Table 5 shows comparison of sequences of cytokine receptor subunits with the primate, e.g., human, DCRS3.1 (50R), and DCRS4.1 (cytor). Both of the new genes are likely alpha type receptor subunits, and thus should bind to ligand without the need for a beta subunit. Based upon structural features, the ligand for the DCRS3 subunits are likely to be a member of the family of cytokines which includes IL-2, IL-4, IL-7, IL-9, and the additional cytokines which signal through IL-2γ common

receptor-like subunits IL-13, IL-15, and the TSLP ligand. Similarly, the ligand for the DCRS4 receptor subunits are probably a ligand in the IL-10 or IFN families, which may be a multi-subunit cytokine, analogous to IL-6 and IL-12.

As used herein, the term DCRS3 shall be used to describe a protein comprising an amino acid sequence shown in Table 1; likewise with DCRS4 and Table 3. In many cases, a substantial fragment thereof will be functionally or structurally equivalent, including, e.g., an extracellular or intracellular domain. The invention also includes a protein variation of a DCRS3 allele whose sequence is provided, e.g., a mutein or soluble extracellular construct. Typically, such agonists or antagonists will exhibit less than about 10% sequence differences, and thus will often have between 1- and 11-fold substitutions, e.g., 2-, 3-, 5-, 7-fold, and others. It also encompasses allelic and other variants, e.g., natural polymorphic, of the protein described. Typically, it will bind to its corresponding biological ligand, perhaps in a dimerized state with an alpha receptor subunit, with high affinity, e.g., at least about 100 nM, usually better than about 30 nM, preferably better than about 10 nM, and more preferably at better than about 3 nM. The term shall also be used herein to refer to related naturally occurring forms, e.g., alleles, polymorphic variants, and metabolic variants of the mammalian protein. Preferred forms of the receptor complexes will bind the appropriate ligand with an affinity and selectivity appropriate for a ligand-receptor interaction.

This invention also encompasses combinations of proteins or peptides having substantial amino acid sequence identity with the amino acid sequences in Tables 1 or 3. It will include sequence variants with relatively few substitutions, e.g., preferably less than about 3-5.

A substantial polypeptide "fragment", or "segment", is a stretch of amino acid residues of at least about 8 amino acids, generally at least 10 amino acids, more generally at least 12 amino acids, often at least 14 amino acids, more often at least 16 amino acids, typically at least 18 amino acids, more

typically at least 20 amino acids, usually at least 22 amino acids, more usually at least 24 amino acids, preferably at least 26 amino acids, more preferably at least 28 amino acids, and, in particularly preferred embodiments, at least about 30 or more amino acids. Sequences of segments of different proteins can be compared to one another over appropriate length stretches. In many situations, fragments may exhibit functional properties of the intact subunits, e.g., the extracellular domain of the transmembrane receptor may retain the ligand binding features, and may be used to prepare a soluble receptor-like complex.

Amino acid sequence homology, or sequence identity, is determined by optimizing residue matches. In some comparisons, gaps may be introduces, as required. See, e.g., Needleham, et al., (1970) J. Mol. Biol. 48:443-453; Sankoff, et al., (1983) chapter one in Time Warps, String Edits, and Macromolecules: The Theory and Practice of Sequence Comparison, Addison-Wesley, Reading, MA; and software packages from IntelliGenetics, Mountain View, CA; and the University of Wisconsin Genetics Computer Group (GCG), Madison, WI; each of which is incorporated herein by reference. This changes when considering conservative substitutions as matches. Conservative substitutions typically include substitutions within the following groups: glycine, alanine; valine, isoleucine, leucine; aspartic acid, glutamic acid; asparagine, glutamine; serine, threonine; lysine, arginine; and phenylalanine, tyrosine. Homologous amino acid sequences are intended to include natural allelic and interspecies variations in the cytokine sequence. Typical homologous proteins or peptides will have from 50-100% homology (if gaps can be introduced), to 60-100% homology (if conservative substitutions are included) with an amino acid sequence segment of Table 1 or 3. Homology measures will be at least about 70%, generally at least 76%, more generally at least 81%, often at least 85%, more often at least 88%, typically at least 90%, more typically at least 92%, usually at least 94%, more usually at least 95%, preferably at least 96%, and more preferably at least 97%, and in particularly preferred embodiments, at least 98% or more. The degree of homology will

vary with the length of the compared segments. Homologous proteins or peptides, such as the allelic variants, will share most biological activities with the embodiments described in Table 1 or 3.

As used herein, the term "biological activity" is used to describe, without limitation, effects on inflammatory responses, innate immunity, and/or morphogenic development by cytokine-like ligands. For example, these receptors should mediate phosphatase or phosphorylase activities, which activities are easily measured by standard procedures. See, e.g., Hardie, et al. (eds. 1995) The Protein Kinase FactBook vols. I and II, Academic Press, San Diego, CA; Hanks, et al. (1991) Meth. Enzymol. 200:38-62; Hunter, et al. (1992) Cell 70:375-388; Lewin (1990) Cell 61:743-752; Pines, et al. (1991) Cold Spring Harbor Symp. Quant. Biol. 56:449-463; and Parker, et al. (1993) Nature 363:736-738. The receptors, or portions thereof, may be useful as phosphate labeling enzymes to label general or specific substrates. The subunits may also be functional immunogens to elicit recognizing antibodies, or antigens capable of binding antibodies.

The terms ligand, agonist, antagonist, and analog of, e.g., a DCRS3, include molecules that modulate the characteristic cellular responses to cytokine ligand proteins, as well as molecules possessing the more standard structural binding competition features of ligand-receptor interactions, e.g., where the receptor is a natural receptor or an antibody. The cellular responses likely are typically mediated through receptor tyrosine kinase pathways.

Also, a ligand is a molecule which serves either as a natural ligand to which said receptor, or an analog thereof, binds, or a molecule which is a functional analog of the natural ligand. The functional analog may be a ligand with structural modifications, or may be a wholly unrelated molecule which has a molecular shape which interacts with the appropriate ligand binding determinants. The ligands may serve as agonists or antagonists, see, e.g., Goodman, et al. (eds. 1990) Goodman &

Gilman's: The Pharmacological Bases of Therapeutics, Pergamon Press, New York.

Rational drug design may also be based upon structural studies of the molecular shapes of a receptor or antibody and other effectors or ligands. See, e.g., Herz, et al. (1997) J. Recept. Signal Transduct. Res. 17:671-776; and Chaiken, et al. (1996) Trends Biotechnol. 14:369-375. Effectors may be other proteins which mediate other functions in response to ligand binding, or other proteins which normally interact with the receptor. One means for determining which sites interact with specific other proteins is a physical structure determination, e.g., x-ray crystallography or 2 dimensional NMR techniques. These will provide guidance as to which amino acid residues form molecular contact regions. For a detailed description of protein structural determination, see, e.g., Blundell and Johnson (1976) Protein Crystallography, Academic Press, New York, which is hereby incorporated herein by reference.

II. Activities

The cytokine receptor-like proteins will have a number of different biological activities, e.g., modulating cell proliferation, or in phosphate metabolism, being added to or removed from specific substrates, typically proteins. Such will generally result in modulation of an inflammatory function, other innate immunity response, or a morphological effect, as typical of cytokine or interleukin signaling. The subunit may have a specific low affinity binding to the ligand.

The receptors may signal through the JAK pathway. See, e.g., Ihle, et al. (1997) Stem Cells 15(suppl. 1):105-111; Silvennoinen, et al. (1997) APMIS 105:497-509; Levy (1997) Cytokine Growth Factor Review 8:81-90; Winston and Hunter (1996) Current Biol. 6:668-671; Barrett (1996) Baillieres Clin. Gastroenterol. 10:1-15; and Briscoe, et al. (1996) Philos. Trans. R. Soc. Lond. B. Biol. Sci. 351:167-171.

The biological activities of the cytokine receptor subunits will be related to addition or removal of phosphate moieties to substrates, typically in a specific manner, but occasionally in

a non specific manner. Substrates may be identified, or conditions for enzymatic activity may be assayed by standard methods, e.g., as described in Hardie, et al. (eds. 1995) The Protein Kinase FactBook vols. I and II, Academic Press, San Diego, CA; Hanks, et al. (1991) Meth. Enzymol. 200:38-62; Hunter, et al. (1992) Cell 70:375-388; Lewin (1990) Cell 61:743-752; Pines, et al. (1991) Cold Spring Harbor Symp. Quant. Biol. 56:449-463; and Parker, et al. (1993) Nature 363:736-738.

The receptor subunits may combine with other subunits, e.g., beta subunits, to form functional complexes, e.g., which may be useful for binding ligand or preparing antibodies. These will have substantial diagnostic uses, including detection or quantitation.

III. Nucleic Acids

This invention contemplates use of isolated nucleic acid or fragments, e.g., which encode these or closely related proteins, or fragments thereof, e.g., to encode a corresponding polypeptide, preferably one which is biologically active. In addition, this invention covers isolated or recombinant DNAs which encode combinations of such proteins or polypeptides having characteristic sequences, e.g., of DCRS3s or DCRS4s. Typically, the nucleic acid is capable of hybridizing, under appropriate conditions, with a nucleic acid sequence segment shown in Tables 1 or 3, but preferably not with a corresponding segment of other receptors, e.g., described in Table 5. Said biologically active protein or polypeptide can be a full length protein, or fragment, and will typically have a segment of amino acid sequence highly homologous, e.g., exhibiting significant stretches of identity, to ones shown in Tables 1 or 3. Further, this invention covers the use of isolated or recombinant nucleic acid, or fragments thereof, which encode proteins having fragments which are equivalent to DCRS3 or DCRS4 proteins. The isolated nucleic acids can have the respective regulatory sequences in the 5' and 3' flanks, e.g., promoters, enhancers, poly-A addition signals, and others from the natural gene. Combinations, as described, are also provided.

An "isolated" nucleic acid is a nucleic acid, e.g., an RNA, DNA, or a mixed polymer, which is substantially pure, e.g., separated from other components which naturally accompany a native sequence, such as ribosomes, polymerases, and flanking genomic sequences from the originating species. The term embraces a nucleic acid sequence which has been removed from its naturally occurring environment, and includes recombinant or cloned DNA isolates, which are thereby distinguishable from naturally occurring compositions, and chemically synthesized analogs or analogs biologically synthesized by heterologous systems. A substantially pure molecule includes isolated forms of the molecule, either completely or substantially pure.

An isolated nucleic acid will generally be a homogeneous composition of molecules, but will, in some embodiments, contain heterogeneity, preferably minor. This heterogeneity is typically found at the polymer ends or portions not critical to a desired biological function or activity.

A "recombinant" nucleic acid is typically defined either by its method of production or its structure. In reference to its method of production, e.g., a product made by a process, the process is use of recombinant nucleic acid techniques, e.g., involving human intervention in the nucleotide sequence. Typically this intervention involves in vitro manipulation, although under certain circumstances it may involve more classical animal breeding techniques. Alternatively, it can be a nucleic acid made by generating a sequence comprising fusion of two fragments which are not naturally contiguous to each other, but is meant to exclude products of nature, e.g., naturally occurring mutants as found in their natural state. Thus, for example, products made by transforming cells with an unnaturally occurring vector is encompassed, as are nucleic acids comprising sequence derived using any synthetic oligonucleotide process. Such a process is often done to replace a codon with a redundant codon encoding the same or a conservative amino acid, while typically introducing or removing a restriction enzyme sequence recognition site. Alternatively, the process is performed to join together nucleic acid segments

of desired functions to generate a single genetic entity comprising a desired combination of functions not found in the commonly available natural forms, e.g., encoding a fusion protein. Restriction enzyme recognition sites are often the target of such artificial manipulations, but other site specific targets, e.g., promoters, DNA replication sites, regulation sequences, control sequences, or other useful features may be incorporated by design. A similar concept is intended for a recombinant, e.g., fusion, polypeptide. This will include a dimeric repeat. Specifically included are synthetic nucleic acids which, by genetic code redundancy, encode equivalent polypeptides to fragments of DCRS3 or DCRS4 and fusions of sequences from various different related molecules, e.g., other cytokine receptor family members.

A "fragment" in a nucleic acid context is a contiguous segment of at least about 17 nucleotides, generally at least 21 nucleotides, more generally at least 25 nucleotides, ordinarily at least 30 nucleotides, more ordinarily at least 35 nucleotides, often at least 39 nucleotides, more often at least 45 nucleotides, typically at least 50 nucleotides, more typically at least 55 nucleotides, usually at least 60 nucleotides, more usually at least 66 nucleotides, preferably at least 72 nucleotides, more preferably at least 79 nucleotides, and in particularly preferred embodiments will be at least 85 or more nucleotides. Typically, fragments of different genetic sequences can be compared to one another over appropriate length stretches, particularly defined segments such as the domains described below.

A nucleic acid which codes for a DCRS3 or DCRS4 will be particularly useful to identify genes, mRNA, and cDNA species which code for itself or closely related proteins, as well as DNAs which code for polymorphic, allelic, or other genetic variants, e.g., from different individuals or related species. Preferred probes for such screens are those regions of the interleukin which are conserved between different polymorphic variants or which contain nucleotides which lack specificity, and will preferably be full length or nearly so. In other

situations, polymorphic variant specific sequences will be more useful.

This invention further covers recombinant nucleic acid molecules and fragments having a nucleic acid sequence identical to or highly homologous to the isolated DNA set forth herein. In particular, the sequences will often be operably linked to DNA segments which control transcription, translation, and DNA replication. These additional segments typically assist in expression of the desired nucleic acid segment.

Homologous, or highly identical, nucleic acid sequences, when compared to one another, e.g., DCRS3 sequences, exhibit significant similarity. The standards for homology in nucleic acids are either measures for homology generally used in the art by sequence comparison or based upon hybridization conditions. Comparative hybridization conditions are described in greater detail below.

Substantial identity in the nucleic acid sequence comparison context means either that the segments, or their complementary strands, when compared, are identical when optimally aligned, with appropriate nucleotide insertions or deletions, in at least about 60% of the nucleotides, generally at least 66%, ordinarily at least 71%, often at least 76%, more often at least 80%, usually at least 84%, more usually at least 88%, typically at least 91%, more typically at least about 93%, preferably at least about 95%, more preferably at least about 96 to 98% or more, and in particular embodiments, as high at about 99% or more of the nucleotides, including, e.g., segments encoding structural domains such as the segments described below. Alternatively, substantial identity will exist when the segments will hybridize under selective hybridization conditions, to a strand or its complement, typically using a sequence derived from Tables 1 or 3. Typically, selective hybridization will occur when there is at least about 55% homology over a stretch of at least about 14 nucleotides, more typically at least about 65%, preferably at least about 75%, and more preferably at least about 90%. See, Kanehisa (1984) <u>Nucl. Acids Res.</u> 12:203-213, which is incorporated herein by

reference. The length of homology comparison, as described, may be over longer stretches, and in certain embodiments will be over a stretch of at least about 17 nucleotides, generally at least about 20 nucleotides, ordinarily at least about 24 nucleotides, usually at least about 28 nucleotides, typically at least about 32 nucleotides, more typically at least about 40 nucleotides, preferably at least about 50 nucleotides, and more preferably at least about 75 to 100 or more nucleotides. This includes, e.g., 125, 150, 175, 200, 225, 250, 275, 300, 325, 350, 375, 400, 425, 450, 475, 500, 525, 544, and other lengths.

Stringent conditions, in referring to homology in the hybridization context, will be stringent combined conditions of salt, temperature, organic solvents, and other parameters typically controlled in hybridization reactions. Stringent temperature conditions will usually include temperatures in excess of about 30 C, more usually in excess of about 37 C, typically in excess of about 45 C, more typically in excess of about 55 C, preferably in excess of about 65 C, and more preferably in excess of about 70 C. Stringent salt conditions will ordinarily be less than about 500 mM, usually less than about 400 mM, more usually less than about 300 mM, typically less than about 200 mM, preferably less than about 100 mM, and more preferably less than about 80 mM, even down to less than about 20 mM. However, the combination of parameters is much more important than the measure of any single parameter. See, e.g., Wetmur and Davidson (1968) J. Mol. Biol. 31:349-370, which is hereby incorporated herein by reference.

The isolated DNA can be readily modified by nucleotide substitutions, nucleotide deletions, nucleotide insertions, and inversions of nucleotide stretches. These modifications result in novel DNA sequences which encode this protein or its derivatives. These modified sequences can be used to produce mutant proteins (muteins) or to enhance the expression of variant species. Enhanced expression may involve gene amplification, increased transcription, increased translation, and other mechanisms. Such mutant DCRS-like derivatives include predetermined or site-specific mutations of the protein or its

fragments, including silent mutations using genetic code degeneracy. "Mutant DCRS3" as used herein encompasses a polypeptide otherwise falling within the homology definition of the DCRS3 as set forth above, but having an amino acid sequence which differs from that of other cytokine receptor-like proteins as found in nature, whether by way of deletion, substitution, or insertion. In particular, "site specific mutant DCRS3" encompasses a protein having substantial sequence identity with a protein of Table 1, and typically shares most of the biological activities or effects of the forms disclosed herein. Likewise in reference to DCRS4.

Although site specific mutation sites are predetermined, mutants need not be site specific. Mammalian DCRS3 mutagenesis can be achieved by making amino acid insertions or deletions in the gene, coupled with expression. Substitutions, deletions, insertions, or many combinations may be generated to arrive at a final construct. Insertions include amino- or carboxy- terminal fusions. Random mutagenesis can be conducted at a target codon and the expressed mammalian DCRS3 mutants can then be screened for the desired activity, providing some aspect of a structure-activity relationship. Methods for making substitution mutations at predetermined sites in DNA having a known sequence are well known in the art, e.g., by M13 primer mutagenesis. See also Sambrook, et al. (1989) and Ausubel, et al. (1987 and periodic Supplements).

The mutations in the DNA normally should not place coding sequences out of reading frames and preferably will not create complementary regions that could hybridize to produce secondary mRNA structure such as loops or hairpins.

The phosphoramidite method described by Beaucage and Carruthers (1981) Tetra. Letts. 22:1859-1862, will produce suitable synthetic DNA fragments. A double stranded fragment will often be obtained either by synthesizing the complementary strand and annealing the strand together under appropriate conditions or by adding the complementary strand using DNA polymerase with an appropriate primer sequence.

Polymerase chain reaction (PCR) techniques can often be applied in mutagenesis. Alternatively, mutagenesis primers are commonly used methods for generating defined mutations at predetermined sites. See, e.g., Innis, et al. (eds. 1990) PCR Protocols: A Guide to Methods and Applications Academic Press, San Diego, CA; and Dieffenbach and Dveksler (1995; eds.) PCR Primer: A Laboratory Manual Cold Spring Harbor Press, CSH, NY.

Certain embodiments of the invention are directed to combination compositions comprising the receptor or ligand sequences described. In other embodiments, functional portions of the sequences may be joined to encode fusion proteins. In other forms, variants of the described sequences may be substituted.

IV. Proteins, Peptides

As described above, the present invention encompasses primate DCRS3, e.g., whose sequences are disclosed in Table 1, and described above. Allelic and other variants are also contemplated, including, e.g., fusion proteins combining portions of such sequences with others, including, e.g., epitope tags and functional domains.

The present invention also provides recombinant proteins, e.g., heterologous fusion proteins using segments from these primate or rodent proteins. A heterologous fusion protein is a fusion of proteins or segments which are naturally not normally fused in the same manner. Thus, the fusion product of a DCRS3 with another cytokine receptor is a continuous protein molecule having sequences fused in a typical peptide linkage, typically made as a single translation product and exhibiting properties, e.g., sequence or antigenicity, derived from each source peptide. A similar concept applies to heterologous nucleic acid sequences. Combinations of various designated proteins into complexes are also provided.

In addition, new constructs may be made from combining similar functional or structural domains from other related proteins, e.g., cytokine receptors or Toll-like receptors, including species variants. For example, ligand-binding or

other segments may be "swapped" between different new fusion polypeptides or fragments. See, e.g., Cunningham, et al. (1989) Science 243:1330-1336; and O'Dowd, et al. (1988) J. Biol. Chem. 263:15985-15992, each of which is incorporated herein by reference. Thus, new chimeric polypeptides exhibiting new combinations of specificities will result from the functional linkage of receptor-binding specificities. For example, the ligand binding domains from other related receptor molecules may be added or substituted for other domains of this or related proteins. The resulting protein will often have hybrid function and properties. For example, a fusion protein may include a targeting domain which may serve to provide sequestering of the fusion protein to a particular subcellular organelle.

Candidate fusion partners and sequences can be selected from various sequence data bases, e.g., GenBank, c/o IntelliGenetics, Mountain View, CA; and BCG, University of Wisconsin Biotechnology Computing Group, Madison, WI, which are each incorporated herein by reference. In particular, combinations of polypeptide sequences provided in Tables 1 and 3 are particularly preferred. Variant forms of the proteins may be substituted in the described combinations.

The present invention particularly provides muteins which bind cytokine-like ligands, and/or which are affected in signal transduction. Structural alignment of human DCRS3 or DCRS4 with other members of the cytokine receptor family show conserved features/residues. See Table 5. Alignment of human DCRS3 or DCRS4 sequence with other members of the cytokine receptor family indicates various structural and functionally shared features. See also, Bazan, et al. (1996) Nature 379:591; Lodi, et al. (1994) Science 263:1762-1766; Sayle and Milner-White (1995) TIBS 20:374-376; and Gronenberg, et al. (1991) Protein Engineering 4:263-269.

Substitutions with either mouse sequences or human sequences are particularly preferred. Conversely, conservative substitutions away from the ligand binding interaction regions will probably preserve most signaling activities; and

conservative substitutions away from the intracellular domains will probably preserve most ligand binding properties.

"Derivatives" of primate DCRS3 include amino acid sequence mutants, glycosylation variants, metabolic derivatives and covalent or aggregative conjugates with other chemical moieties. Covalent derivatives can be prepared by linkage of functionalities to groups which are found in DCRS3 amino acid side chains or at the N- or C- termini, e.g., by means which are well known in the art. These derivatives can include, without limitation, aliphatic esters or amides of the carboxyl terminus, or of residues containing carboxyl side chains, O-acyl derivatives of hydroxyl group-containing residues, and N-acyl derivatives of the amino terminal amino acid or amino-group containing residues, e.g., lysine or arginine. Acyl groups are selected from the group of alkyl-moieties, including C3 to C18 normal alkyl, thereby forming alkanoyl aroyl species.

In particular, glycosylation alterations are included, e.g., made by modifying the glycosylation patterns of a polypeptide during its synthesis and processing, or in further processing steps. Particularly preferred means for accomplishing this are by exposing the polypeptide to glycosylating enzymes derived from cells which normally provide such processing, e.g., mammalian glycosylation enzymes. Deglycosylation enzymes are also contemplated. Also embraced are versions of the same primary amino acid sequence which have other minor modifications, including phosphorylated amino acid residues, e.g., phosphotyrosine, phosphoserine, or phosphothreonine.

A major group of derivatives are covalent conjugates of the receptors or fragments thereof with other proteins of polypeptides. These derivatives can be synthesized in recombinant culture such as N- or C-terminal fusions or by the use of agents known in the art for their usefulness in cross-linking proteins through reactive side groups. Preferred derivatization sites with cross-linking agents are at free amino groups, carbohydrate moieties, and cysteine residues.

Fusion polypeptides between the receptors and other homologous or heterologous proteins are also provided. Homologous polypeptides may be fusions between different receptors, resulting in, for instance, a hybrid protein exhibiting binding specificity for multiple different cytokine ligands, or a receptor which may have broadened or weakened specificity of substrate effect. Likewise, heterologous fusions may be constructed which would exhibit a combination of properties or activities of the derivative proteins. Typical examples are fusions of a reporter polypeptide, e.g., luciferase, with a segment or domain of a receptor, e.g., a ligand-binding segment, so that the presence or location of a desired ligand may be easily determined. See, e.g., Dull, et al., U.S. Patent No. 4,859,609, which is hereby incorporated herein by reference. Other gene fusion partners include glutathione-S-transferase (GST), bacterial ß-galactosidase, trpE, Protein A, ß-lactamase, alpha amylase, alcohol dehydrogenase, and yeast alpha mating factor. See, e.g., Godowski, et al. (1988) Science 241:812-816. Labeled proteins will often be substituted in the described combinations of proteins.

The phosphoramidite method described by Beaucage and Carruthers (1981) Tetra. Letts. 22:1859-1862, will produce suitable synthetic DNA fragments. A double stranded fragment will often be obtained either by synthesizing the complementary strand and annealing the strand together under appropriate conditions or by adding the complementary strand using DNA polymerase with an appropriate primer sequence.

Such polypeptides may also have amino acid residues which have been chemically modified by phosphorylation, sulfonation, biotinylation, or the addition or removal of other moieties, particularly those which have molecular shapes similar to phosphate groups. In some embodiments, the modifications will be useful labeling reagents, or serve as purification targets, e.g., affinity ligands.

Fusion proteins will typically be made by either recombinant nucleic acid methods or by synthetic polypeptide

methods. Techniques for nucleic acid manipulation and expression are described generally, for example, in Sambrook, et al. (1989) Molecular Cloning: A Laboratory Manual (2d ed.), Vols. 1-3, Cold Spring Harbor Laboratory, and Ausubel, et al. (eds. 1987 and periodic supplements) Current Protocols in Molecular Biology, Greene/Wiley, New York, which are each incorporated herein by reference. Techniques for synthesis of polypeptides are described, for example, in Merrifield (1963) J. Amer. Chem. Soc. 85:2149-2156; Merrifield (1986) Science 232: 341-347; and Atherton, et al. (1989) Solid Phase Peptide Synthesis: A Practical Approach, IRL Press, Oxford; each of which is incorporated herein by reference. See also Dawson, et al. (1994) Science 266:776-779 for methods to make larger polypeptides.

This invention also contemplates the use of derivatives of a DCRS3 or DCRS4 other than variations in amino acid sequence or glycosylation. Such derivatives may involve covalent or aggregative association with chemical moieties. These derivatives generally fall into three classes: (1) salts, (2) side chain and terminal residue covalent modifications, and (3) adsorption complexes, for example with cell membranes. Such covalent or aggregative derivatives are useful as immunogens, as reagents in immunoassays, or in purification methods such as for affinity purification of a receptor or other binding molecule, e.g., an antibody. For example, a cytokine ligand can be immobilized by covalent bonding to a solid support such as cyanogen bromide-activated Sepharose, by methods which are well known in the art, or adsorbed onto polyolefin surfaces, with or without glutaraldehyde cross-linking, for use in the assay or purification of a cytokine receptor, antibodies, or other similar molecules. The ligand can also be labeled with a detectable group, for example radioiodinated by the chloramine T procedure, covalently bound to rare earth chelates, or conjugated to another fluorescent moiety for use in diagnostic assays.

A combination, e.g., including a DCRS3 or DCRS4, of this invention can be used as an immunogen for the production of

antisera or antibodies specific, e.g., capable of distinguishing between other cytokine receptor family members, for the combinations described. The complexes can be used to screen monoclonal antibodies or antigen-binding fragments prepared by immunization with various forms of impure preparations containing the protein. In particular, the term "antibodies" also encompasses antigen binding fragments of natural antibodies, e.g., Fab, Fab2, Fv, etc. A purified DCRS3 can also be used as a reagent to detect antibodies generated in response to the presence of elevated levels of expression, or immunological disorders which lead to antibody production to the endogenous receptor. Additionally, DCRS3 fragments may also serve as immunogens to produce the antibodies of the present invention, as described immediately below. For example, this invention contemplates antibodies having binding affinity to or being raised against the amino acid sequences shown in Table 1, fragments thereof, or various homologous peptides. In particular, this invention contemplates antibodies having binding affinity to, or having been raised against, specific fragments which are predicted to be, or actually are, exposed at the exterior protein surface of a native DCRS3. Complexes of combinations of proteins will also be useful, and antibody preparations thereto can be made.

The blocking of physiological response to the receptor ligands may result from the inhibition of binding of the ligand to the receptor, likely through competitive inhibition. Thus, in vitro assays of the present invention will often use antibodies or antigen binding segments of these antibodies, or fragments attached to solid phase substrates. These assays will also allow for the diagnostic determination of the effects of either ligand binding region mutations and modifications, or other mutations and modifications, e.g., which affect signaling or enzymatic function.

This invention also contemplates the use of competitive drug screening assays, e.g., where neutralizing antibodies to the receptor complexes or fragments compete with a test compound for binding to a ligand or other antibody. In this manner, the

neutralizing antibodies or fragments can be used to detect the presence of a polypeptide which shares one or more binding sites to a receptor and can also be used to occupy binding sites on a receptor that might otherwise bind a ligand.

V. Making Nucleic Acids and Protein

DNA which encodes the protein or fragments thereof can be obtained by chemical synthesis, screening cDNA libraries, or by screening genomic libraries prepared from a wide variety of cell lines or tissue samples. Natural sequences can be isolated using standard methods and the sequences provided herein, e.g., in Tables 1 or 3. Other species counterparts can be identified by hybridization techniques, or by various PCR techniques, combined with or by searching in sequence databases, e.g., GenBank.

This DNA can be expressed in a wide variety of host cells for the synthesis of a full-length receptor or fragments which can in turn, for example, be used to generate polyclonal or monoclonal antibodies; for binding studies; for construction and expression of modified ligand binding or kinase/phosphatase domains; and for structure/function studies. Variants or fragments can be expressed in host cells that are transformed or transfected with appropriate expression vectors. These molecules can be substantially free of protein or cellular contaminants, other than those derived from the recombinant host, and therefore are particularly useful in pharmaceutical compositions when combined with a pharmaceutically acceptable carrier and/or diluent. The protein, or portions thereof, may be expressed as fusions with other proteins. Combinations of the described proteins, or nucleic acids encoding them, are particularly interesting.

Expression vectors are typically self-replicating DNA or RNA constructs containing the desired receptor gene or its fragments, usually operably linked to suitable genetic control elements that are recognized in a suitable host cell. These control elements are capable of effecting expression within a suitable host. The multiple genes may be coordinately

expressed, and may be on a polycistronic message. The specific type of control elements necessary to effect expression will depend upon the eventual host cell used. Generally, the genetic control elements can include a prokaryotic promoter system or a eukaryotic promoter expression control system, and typically include a transcriptional promoter, an optional operator to control the onset of transcription, transcription enhancers to elevate the level of mRNA expression, a sequence that encodes a suitable ribosome binding site, and sequences that terminate transcription and translation. Expression vectors also usually contain an origin of replication that allows the vector to replicate independently of the host cell.

The vectors of this invention include those which contain DNA which encodes a combination of proteins, as described, or a biologically active equivalent polypeptide. The DNA can be under the control of a viral promoter and can encode a selection marker. This invention further contemplates use of such expression vectors which are capable of expressing eukaryotic cDNAs coding for such proteins in a prokaryotic or eukaryotic host, where the vector is compatible with the host and where the eukaryotic cDNAs are inserted into the vector such that growth of the host containing the vector expresses the cDNAs in question. Usually, expression vectors are designed for stable replication in their host cells or for amplification to greatly increase the total number of copies of the desirable gene per cell. It is not always necessary to require that an expression vector replicate in a host cell, e.g., it is possible to effect transient expression of the protein or its fragments in various hosts using vectors that do not contain a replication origin that is recognized by the host cell. It is also possible to use vectors that cause integration of the protein encoding portions into the host DNA by recombination.

Vectors, as used herein, comprise plasmids, viruses, bacteriophage, integratable DNA fragments, and other vehicles which enable the integration of DNA fragments into the genome of the host. Expression vectors are specialized vectors which contain genetic control elements that effect expression of

operably linked genes. Plasmids are the most commonly used form of vector but all other forms of vectors which serve an equivalent function and which are, or become, known in the art are suitable for use herein. See, e.g., Pouwels, et al. (1985 and Supplements) Cloning Vectors: A Laboratory Manual, Elsevier, N.Y., and Rodriguez, et al. (eds. 1988) Vectors: A Survey of Molecular Cloning Vectors and Their Uses, Buttersworth, Boston, which are incorporated herein by reference.

Transformed cells are cells, preferably mammalian, that have been transformed or transfected with vectors constructed using recombinant DNA techniques. Transformed host cells usually express the desired proteins, but for purposes of cloning, amplifying, and manipulating its DNA, do not need to express the subject proteins. This invention further contemplates culturing transformed cells in a nutrient medium, thus permitting the proteins to accumulate. The proteins can be recovered, either from the culture or, in certain instances, from the culture medium.

For purposes of this invention, nucleic sequences are operably linked when they are functionally related to each other. For example, DNA for a presequence or secretory leader is operably linked to a polypeptide if it is expressed as a preprotein or participates in directing the polypeptide to the cell membrane or in secretion of the polypeptide. A promoter is operably linked to a coding sequence if it controls the transcription of the polypeptide; a ribosome binding site is operably linked to a coding sequence if it is positioned to permit translation. Usually, operably linked means contiguous and in reading frame, however, certain genetic elements such as repressor genes are not contiguously linked but still bind to operator sequences that in turn control expression.

Suitable host cells include prokaryotes, lower eukaryotes, and higher eukaryotes. Prokaryotes include both gram negative and gram positive organisms, e.g., E. coli and B. subtilis. Lower eukaryotes include yeasts, e.g., S. cerevisiae and Pichia, and species of the genus Dictyostelium. Higher eukaryotes include established tissue culture cell lines from animal cells,

both of non-mammalian origin, e.g., insect cells, and birds, and of mammalian origin, e.g., human, primates, and rodents.

Prokaryotic host-vector systems include a wide variety of vectors for many different species. As used herein, E. coli and its vectors will be used generically to include equivalent vectors used in other prokaryotes. A representative vector for amplifying DNA is pBR322 or many of its derivatives. Vectors that can be used to express the receptor or its fragments include, but are not limited to, such vectors as those containing the lac promoter (pUC-series); trp promoter (pBR322-trp); Ipp promoter (the pIN-series); lambda-pP or pR promoters (pOTS); or hybrid promoters such as ptac (pDR540). See Brosius, et al. (1988) "Expression Vectors Employing Lambda-, trp-, lac-, and Ipp-derived Promoters", in Vectors: A Survey of Molecular Cloning Vectors and Their Uses, (eds. Rodriguez and Denhardt), Buttersworth, Boston, Chapter 10, pp. 205-236, which is incorporated herein by reference.

Lower eukaryotes, e.g., yeasts and Dictyostelium, may be transformed with DCRS3 or DCRS4 sequence containing vectors. For purposes of this invention, the most common lower eukaryotic host is the baker's yeast, Saccharomyces cerevisiae. It will be used to generically represent lower eukaryotes although a number of other strains and species are also available. Yeast vectors typically consist of a replication origin (unless of the integrating type), a selection gene, a promoter, DNA encoding the receptor or its fragments, and sequences for translation termination, polyadenylation, and transcription termination. Suitable expression vectors for yeast include such constitutive promoters as 3-phosphoglycerate kinase and various other glycolytic enzyme gene promoters or such inducible promoters as the alcohol dehydrogenase 2 promoter or metallothionine promoter. Suitable vectors include derivatives of the following types: self-replicating low copy number (such as the YRp-series), self-replicating high copy number (such as the YEp-series); integrating types (such as the YIp-series), or mini-chromosomes (such as the YCp-series).

Higher eukaryotic tissue culture cells are normally the preferred host cells for expression of the functionally active interleukin or receptor proteins. In principle, many higher eukaryotic tissue culture cell lines are workable, e.g., insect baculovirus expression systems, whether from an invertebrate or vertebrate source. However, mammalian cells are preferred. Transformation or transfection and propagation of such cells has become a routine procedure. Examples of useful cell lines include HeLa cells, Chinese hamster ovary (CHO) cell lines, baby rat kidney (BRK) cell lines, insect cell lines, bird cell lines, and monkey (COS) cell lines. Expression vectors for such cell lines usually include an origin of replication, a promoter, a translation initiation site, RNA splice sites (if genomic DNA is used), a polyadenylation site, and a transcription termination site. These vectors also usually contain a selection gene or amplification gene. Suitable expression vectors may be plasmids, viruses, or retroviruses carrying promoters derived, e.g., from such sources as from adenovirus, SV40, parvoviruses, vaccinia virus, or cytomegalovirus. Representative examples of suitable expression vectors include pCDNA1; pCD, see Okayama, et al. (1985) Mol. Cell Biol. 5:1136-1142; pMClneo PolyA, see Thomas, et al. (1987) Cell 51:503-512; and a baculovirus vector such as pAC 373 or pAC 610.

For secreted proteins and some membrane proteins, an open reading frame usually encodes a polypeptide that consists of a mature or secreted product covalently linked at its N-terminus to a signal peptide. The signal peptide is cleaved prior to secretion of the mature, or active, polypeptide. The cleavage site can be predicted with a high degree of accuracy from empirical rules, e.g., von-Heijne (1986) Nucleic Acids Research 14:4683-4690 and Nielsen, et al. (1997) Protein Eng. 10:1-12, and the precise amino acid composition of the signal peptide often does not appear to be critical to its function, e.g., Randall, et al. (1989) Science 243:1156-1159; Kaiser et al. (1987) Science 235:312-317. The mature proteins of the invention can be readily determined using standard methods.

It will often be desired to express these polypeptides in a system which provides a specific or defined glycosylation pattern. In this case, the usual pattern will be that provided naturally by the expression system. However, the pattern will be modifiable by exposing the polypeptide, e.g., an unglycosylated form, to appropriate glycosylating proteins introduced into a heterologous expression system. For example, the receptor gene may be co-transformed with one or more genes encoding mammalian or other glycosylating enzymes. Using this approach, certain mammalian glycosylation patterns will be achievable in prokaryote or other cells. Expression in prokaryote cells will typically lead to unglycosylated forms of protein.

The source of DCRS3 or DCRS4 can be a eukaryotic or prokaryotic host expressing recombinant DCRS, such as is described above. The source can also be a cell line, but other mammalian cell lines are also contemplated by this invention, with the preferred cell line being from the human species.

Now that the sequences are known, a primate DCRS3 or DCRS4, fragments, or derivatives thereof can be prepared by conventional processes for synthesizing peptides. These include processes such as are described in Stewart and Young (1984) Solid Phase Peptide Synthesis, Pierce Chemical Co., Rockford, IL; Bodanszky and Bodanszky (1984) The Practice of Peptide Synthesis, Springer-Verlag, New York; and Bodanszky (1984) The Principles of Peptide Synthesis, Springer-Verlag, New York; all of each which are incorporated herein by reference. For example, an azide process, an acid chloride process, an acid anhydride process, a mixed anhydride process, an active ester process (for example, p-nitrophenyl ester, N-hydroxysuccinimide ester, or cyanomethyl ester), a carbodiimidazole process, an oxidative-reductive process, or a dicyclohexylcarbodiimide (DCCD)/additive process can be used. Solid phase and solution phase syntheses are both applicable to the foregoing processes. Similar techniques can be used with partial DCRS3 or DCRS4 sequences.

DCRS3 or DCRS4 proteins, fragments, or derivatives are suitably prepared in accordance with the above processes as typically employed in peptide synthesis, generally either by a so-called stepwise process which comprises condensing an amino acid to the terminal amino acid, one by one in sequence, or by coupling peptide fragments to the terminal amino acid. Amino groups that are not being used in the coupling reaction typically must be protected to prevent coupling at an incorrect location.

If a solid phase synthesis is adopted, the C-terminal amino acid is bound to an insoluble carrier or support through its carboxyl group. The insoluble carrier is not particularly limited as long as it has a binding capability to a reactive carboxyl group. Examples of such insoluble carriers include halomethyl resins, such as chloromethyl resin or bromomethyl resin, hydroxymethyl resins, phenol resins, tert-alkyloxycarbonylhydrazidated resins, and the like.

An amino group-protected amino acid is bound in sequence through condensation of its activated carboxyl group and the reactive amino group of the previously formed peptide or chain, to synthesize the peptide step by step. After synthesizing the complete sequence, the peptide is split off from the insoluble carrier to produce the peptide. This solid-phase approach is generally described by Merrifield, et al. (1963) in J. Am. Chem. Soc. 85:2149-2156, which is incorporated herein by reference.

The prepared protein and fragments thereof can be isolated and purified from the reaction mixture by means of peptide separation, for example, by extraction, precipitation, electrophoresis, various forms of chromatography, and the like. The receptors of this invention can be obtained in varying degrees of purity depending upon desired uses. Purification can be accomplished by use of the protein purification techniques disclosed herein, see below, or by the use of the antibodies herein described in methods of immunoabsorbant affinity chromatography. This immunoabsorbant affinity chromatography is carried out by first linking the antibodies to a solid support and then contacting the linked antibodies with solubilized

lysates of appropriate cells, lysates of other cells expressing the receptor, or lysates or supernatants of cells producing the protein as a result of DNA techniques, see below.

Generally, the purified protein will be at least about 40% pure, ordinarily at least about 50% pure, usually at least about 60% pure, typically at least about 70% pure, more typically at least about 80% pure, preferable at least about 90% pure and more preferably at least about 95% pure, and in particular embodiments, 97%-99% or more. Purity will usually be on a weight basis, but can also be on a molar basis. Different assays will be applied as appropriate. Individual proteins may be purified and thereafter combined.

VI. Antibodies

Antibodies can be raised to various mammalian, e.g., primate DCRS3 or DCRS4 proteins and fragments thereof, both in naturally occurring native forms and in their recombinant forms, the difference being that antibodies to the active receptor are more likely to recognize epitopes which are only present in the native conformations. Denatured antigen detection can also be useful in, e.g., Western analysis. Anti-idiotypic antibodies are also contemplated, which would be useful as agonists or antagonists of a natural receptor or an antibody.

Antibodies, including binding fragments and single chain versions, against predetermined fragments of the protein can be raised by immunization of animals with conjugates of the fragments with immunogenic proteins. Monoclonal antibodies are prepared from cells secreting the desired antibody. These antibodies can be screened for binding to normal or defective protein, or screened for agonistic or antagonistic activity. These monoclonal antibodies will usually bind with at least a K_D of about 1 mM, more usually at least about 300 μM, typically at least about 100μM, more typically at least about 30 μM, preferably at least about 10 μM, and more preferably at least about 3 μM or better.

The antibodies, including antigen binding fragments, of this invention can have significant diagnostic or therapeutic

value. They can be potent antagonists that bind to the receptor and inhibit binding to ligand or inhibit the ability of the receptor to elicit a biological response, e.g., act on its substrate. They also can be useful as non-neutralizing antibodies and can be coupled to toxins or radionuclides to bind producing cells, or cells localized to the source of the interleukin. Further, these antibodies can be conjugated to drugs or other therapeutic agents, either directly or indirectly by means of a linker.

The antibodies of this invention can also be useful in diagnostic applications. As capture or non-neutralizing antibodies, they might bind to the receptor without inhibiting ligand or substrate binding. As neutralizing antibodies, they can be useful in competitive binding assays. They will also be useful in detecting or quantifying ligand. They may be used as reagents for Western blot analysis, or for immunoprecipitation or immunopurification of the respective protein. Likewise, nucleic acids and proteins may be immobilized to solid substrates for affinity purification or detection methods. The substrates may be, e.g., solid resin beads or sheets of plastic.

Protein fragments may be joined to other materials, particularly polypeptides, as fused or covalently joined polypeptides to be used as immunogens. Mammalian cytokine receptors and fragments may be fused or covalently linked to a variety of immunogens, such as keyhole limpet hemocyanin, bovine serum albumin, tetanus toxoid, etc. See Microbiology, Hoeber Medical Division, Harper and Row, 1969; Landsteiner (1962) Specificity of Serological Reactions, Dover Publications, New York; and Williams, et al. (1967) Methods in Immunology and Immunochemistry, Vol. 1, Academic Press, New York; each of which are incorporated herein by reference, for descriptions of methods of preparing polyclonal antisera. A typical method involves hyperimmunization of an animal with an antigen. The blood of the animal is then collected shortly after the repeated immunizations and the gamma globulin is isolated.

In some instances, it is desirable to prepare monoclonal antibodies from various mammalian hosts, such as mice, rodents,

primates, humans, etc. Description of techniques for preparing such monoclonal antibodies may be found in, e.g., Stites, et al. (eds.) Basic and Clinical Immunology (4th ed.), Lange Medical Publications, Los Altos, CA, and references cited therein; Harlow and Lane (1988) Antibodies: A Laboratory Manual, CSH Press; Goding (1986) Monoclonal Antibodies: Principles and Practice (2d ed.) Academic Press, New York; and particularly in Kohler and Milstein (1975) in Nature 256: 495-497, which discusses one method of generating monoclonal antibodies. Each of these references is incorporated herein by reference. Summarized briefly, this method involves injecting an animal with an immunogen. The animal is then sacrificed and cells taken from its spleen, which are then fused with myeloma cells. The result is a hybrid cell or "hybridoma" that is capable of reproducing *in vitro*. The population of hybridomas is then screened to isolate individual clones, each of which secrete a single antibody species to the immunogen. In this manner, the individual antibody species obtained are the products of immortalized and cloned single B cells from the immune animal generated in response to a specific site recognized on the immunogenic substance.

Other suitable techniques involve *in vitro* exposure of lymphocytes to the antigenic polypeptides or alternatively to selection of libraries of antibodies in phage or similar vectors. See, Huse, et al. (1989) "Generation of a Large Combinatorial Library of the Immunoglobulin Repertoire in Phage Lambda," Science 246:1275-1281; and Ward, et al. (1989) Nature 341:544-546, each of which is hereby incorporated herein by reference. The polypeptides and antibodies of the present invention may be used with or without modification, including chimeric or humanized antibodies. Frequently, the polypeptides and antibodies will be labeled by joining, either covalently or non-covalently, a substance which provides for a detectable signal. A wide variety of labels and conjugation techniques are known and are reported extensively in both the scientific and patent literature. Suitable labels include radionuclides, enzymes, substrates, cofactors, inhibitors, fluorescent

moieties, chemiluminescent moieties, magnetic particles, and the like. Patents, teaching the use of such labels include U.S. Patent Nos. 3,817,837; 3,850,752; 3,939,350; 3,996,345; 4,277,437; 4,275,149; and 4,366,241. Also, recombinant or chimeric immunoglobulins may be produced, see Cabilly, U.S. Patent No. 4,816,567; or made in transgenic mice, see Mendez, et al. (1997) Nature Genetics 15:146-156. These references are incorporated herein by reference.

The antibodies of this invention can also be used for affinity chromatography in isolating DCRS3 proteins or peptides. Columns can be prepared where the antibodies are linked to a solid support, e.g., particles, such as agarose, Sephadex, or the like, where a cell lysate may be passed through the column, the column washed, followed by increasing concentrations of a mild denaturant, whereby the purified protein will be released. Alternatively, the protein may be used to purify antibody. Appropriate cross absorptions or depletions may be applied.

The antibodies may also be used to screen expression libraries for particular expression products. Usually the antibodies used in such a procedure will be labeled with a moiety allowing easy detection of presence of antigen by antibody binding.

Antibodies raised against a cytokine receptor will also be used to raise anti-idiotypic antibodies. These will be useful in detecting or diagnosing various immunological conditions related to expression of the protein or cells which express the protein. They also will be useful as agonists or antagonists of the ligand, which may be competitive inhibitors or substitutes for naturally occurring ligands.

A cytokine receptor protein that specifically binds to or that is specifically immunoreactive with an antibody generated against a defined immunogen, such as an immunogen consisting of the amino acid sequence of SEQ ID NO: 2, 25, 5, 28, or 31, is typically determined in an immunoassay. The immunoassay typically uses a polyclonal antiserum which was raised, e.g., to a protein of SEQ ID NO: 2, 25, 5, 28, or 31. This antiserum is selected to have low crossreactivity against other cytokine

receptor family members, e.g., IL-11 receptor subunit alpha, IL-6 receptor subunit alpha, or p40, preferably from the same species, and any such crossreactivity is removed by immunoabsorption prior to use in the immunoassay.

In order to produce antisera for use in an immunoassay, the protein, e.g., of SEQ ID NO: 2, 25, 5, 28, or 31, is isolated as described herein. For example, recombinant protein may be produced in a mammalian cell line. An appropriate host, e.g., an inbred strain of mice such as Balb/c, is immunized with the selected protein, typically using a standard adjuvant, such as Freund's adjuvant, and a standard mouse immunization protocol (see Harlow and Lane, supra). Alternatively, a synthetic peptide derived from the sequences disclosed herein and conjugated to a carrier protein can be used an immunogen. Polyclonal sera are collected and titered against the immunogen protein in an immunoassay, e.g., a solid phase immunoassay with the immunogen immobilized on a solid support. Polyclonal antisera with a titer of 10^4 or greater are selected and tested for their cross reactivity against other cytokine receptor family members, e.g., IL-2, IL-7, IL-9, or EPO receptor subunit, using a competitive binding immunoassay such as the one described in Harlow and Lane, supra, at pages 570-573. Preferably at least two cytokine receptor family members are used in this determination. These cytokine receptor family members can be produced as recombinant proteins and isolated using standard molecular biology and protein chemistry techniques as described herein.

Immunoassays in the competitive binding format can be used for the crossreactivity determinations. For example, the protein of SEQ ID NO: 2, 25, 5, 28, or 31 can be immobilized to a solid support. Proteins added to the assay compete with the binding of the antisera to the immobilized antigen. The ability of the above proteins to compete with the binding of the antisera to the immobilized protein is compared to the proteins, e.g., of IL-2, IL-7, IL-9, or EPO receptor subunit. The percent crossreactivity for the above proteins is calculated, using standard calculations. Those antisera with less than 10%

crossreactivity with each of the proteins listed above are selected and pooled. The cross-reacting antibodies are then removed from the pooled antisera by immunoabsorption with the above-listed proteins.

The immunoabsorbed and pooled antisera are then used in a competitive binding immunoassay as described above to compare a second protein to the immunogen protein (e.g., DCRS3 like protein of SEQ ID NO: 2). In order to make this comparison, the two proteins are each assayed at a wide range of concentrations and the amount of each protein required to inhibit 50% of the binding of the antisera to the immobilized protein is determined. If the amount of the second protein required is less than twice the amount of the protein of the selected protein or proteins that is required, then the second protein is said to specifically bind to an antibody generated to the immunogen.

It is understood that these cytokine receptor proteins are members of a family of homologous proteins that comprise at least 6 so far identified genes. For a particular gene product, such as a DCRS3 or DCRS4, the term refers not only to the amino acid sequences disclosed herein, but also to other proteins that are allelic, non-allelic, or species variants. It is also understood that the terms include nonnatural mutations introduced by deliberate mutation using conventional recombinant technology such as single site mutation, or by excising short sections of DNA encoding the respective proteins, or by substituting new amino acids, or adding new amino acids. Such minor alterations typically will substantially maintain the immunoidentity of the original molecule and/or its biological activity. Thus, these alterations include proteins that are specifically immunoreactive with a designated naturally occurring DCRS3 or DCRS4 protein. The biological properties of the altered proteins can be determined by expressing the protein in an appropriate cell line and measuring the appropriate effect, e.g., upon transfected lymphocytes. Particular protein modifications considered minor would include conservative substitution of amino acids with similar chemical properties, as

described above for the cytokine receptor family as a whole. By aligning a protein optimally with the protein of the cytokine receptors and by using the conventional immunoassays described herein to determine immunoidentity, one can determine the protein compositions of the invention.

VII. Kits and quantitation

Both naturally occurring and recombinant forms of the cytokine receptor like molecules of this invention are particularly useful in kits and assay methods. For example, these methods would also be applied to screening for binding activity, e.g., ligands for these proteins. Several methods of automating assays have been developed in recent years so as to permit screening of tens of thousands of compounds per year. See, e.g., a BIOMEK automated workstation, Beckman Instruments, Palo Alto, California, and Fodor, et al. (1991) Science 251:767-773, which is incorporated herein by reference. The latter describes means for testing binding by a plurality of defined polymers synthesized on a solid substrate. The development of suitable assays to screen for a ligand or agonist/antagonist homologous proteins can be greatly facilitated by the availability of large amounts of purified, soluble cytokine receptors in an active state such as is provided by this invention.

Purified DCRS3 or DCRS4 can be coated directly onto plates for use in the aforementioned ligand screening techniques. However, non-neutralizing antibodies to these proteins can be used as capture antibodies to immobilize the respective receptor on the solid phase, useful, e.g., in diagnostic uses.

This invention also contemplates use of DCRS3 or DCRS4, fragments thereof, peptides, and their fusion products in a variety of diagnostic kits and methods for detecting the presence of the protein or its ligand. Alternatively, or additionally, antibodies against the molecules may be incorporated into the kits and methods. Typically the kit will have a compartment containing either a DCRS3 or DCRS4 peptide or gene segment or a reagent which recognizes one or the other.

Typically, recognition reagents, in the case of peptide, would be a receptor or antibody, or in the case of a gene segment, would usually be a hybridization probe.

A preferred kit for determining the concentration of, e.g., DCRS3 in a sample would typically comprise a labeled compound, e.g., ligand or antibody, having known binding affinity for DCRS3, a source of DCRS3 (naturally occurring or recombinant) as a positive control, and a means for separating the bound from free labeled compound, for example a solid phase for immobilizing DCRS3 in the test sample. Compartments containing reagents, and instructions, will normally be provided. Appropriate nucleic acid or protein containing kits are also provided.

Antibodies, including antigen binding fragments, specific for mammalian DCRS3 or a peptide fragment, or receptor fragments are useful in diagnostic applications to detect the presence of elevated levels of ligand and/or its fragments. Diagnostic assays may be homogeneous (without a separation step between free reagent and antibody-antigen complex) or heterogeneous (with a separation step). Various commercial assays exist, such as radioimmunoassay (RIA), enzyme-linked immunosorbent assay (ELISA), enzyme immunoassay (EIA), enzyme-multiplied immunoassay technique (EMIT), substrate-labeled fluorescent immunoassay (SLFIA) and the like. For example, unlabeled antibodies can be employed by using a second antibody which is labeled and which recognizes the antibody to a cytokine receptor or to a particular fragment thereof. These assays have also been extensively discussed in the literature. See, e.g., Harlow and Lane (1988) Antibodies: A Laboratory Manual, CSH., and Coligan (ed. 1991 and periodic supplements) Current Protocols In Immunology Greene/Wiley, New York.

Anti-idiotypic antibodies may have similar use to serve as agonists or antagonists of cytokine receptors. These should be useful as therapeutic reagents under appropriate circumstances.

Frequently, the reagents for diagnostic assays are supplied in kits, so as to optimize the sensitivity of the assay. For the subject invention, depending upon the nature of the assay,

the protocol, and the label, either labeled or unlabeled antibody, or labeled ligand is provided. This is usually in conjunction with other additives, such as buffers, stabilizers, materials necessary for signal production such as substrates for enzymes, and the like. Preferably, the kit will also contain instructions for proper use and disposal of the contents after use. Typically the kit has compartments for each useful reagent, and will contain instructions for proper use and disposal of reagents. Desirably, the reagents are provided as a dry lyophilized powder, where the reagents may be reconstituted in an aqueous medium having appropriate concentrations for performing the assay.

The aforementioned constituents of the diagnostic assays may be used without modification or may be modified in a variety of ways. For example, labeling may be achieved by covalently or non-covalently joining a moiety which directly or indirectly provides a detectable signal. In many of these assays, a test compound, cytokine receptor, or antibodies thereto can be labeled either directly or indirectly. Possibilities for direct labeling include label groups: radiolabels such as ^{125}I, enzymes (U.S. Pat. No. 3,645,090) such as peroxidase and alkaline phosphatase, and fluorescent labels (U.S. Pat. No. 3,940,475) capable of monitoring the change in fluorescence intensity, wavelength shift, or fluorescence polarization. Both of the patents are incorporated herein by reference. Possibilities for indirect labeling include biotinylation of one constituent followed by binding to avidin coupled to one of the above label groups.

There are also numerous methods of separating the bound from the free ligand, or alternatively the bound from the free test compound. The cytokine receptor can be immobilized on various matrixes followed by washing. Suitable matrices include plastic such as an ELISA plate, filters, and beads. Methods of immobilizing the receptor to a matrix include, without limitation, direct adhesion to plastic, use of a capture antibody, chemical coupling, and biotin-avidin. The last step in this approach involves the precipitation of antibody/antigen

complex by any of several methods including those utilizing, e.g., an organic solvent such as polyethylene glycol or a salt such as ammonium sulfate. Other suitable separation techniques include, without limitation, the fluorescein antibody magnetizable particle method described in Rattle, et al. (1984) Clin. Chem. 30:1457-1461, and the double antibody magnetic particle separation as described in U.S. Pat. No. 4,659,678, each of which is incorporated herein by reference.

The methods for linking protein or fragments to various labels have been extensively reported in the literature and do not require detailed discussion here. Many of the techniques involve the use of activated carboxyl groups either through the use of carbodiimide or active esters to form peptide bonds, the formation of thioethers by reaction of a mercapto group with an activated halogen such as chloroacetyl, or an activated olefin such as maleimide, for linkage, or the like. Fusion proteins will also find use in these applications.

Another diagnostic aspect of this invention involves use of oligonucleotide or polynucleotide sequences taken from the sequence of an cytokine receptor. These sequences can be used as probes for detecting levels of the respective cytokine receptor in patients suspected of having an immunological disorder. The preparation of both RNA and DNA nucleotide sequences, the labeling of the sequences, and the preferred size of the sequences has received ample description and discussion in the literature. Normally an oligonucleotide probe should have at least about 14 nucleotides, usually at least about 18 nucleotides, and the polynucleotide probes may be up to several kilobases. Various labels may be employed, most commonly radionuclides, particularly ^{32}P. However, other techniques may also be employed, such as using biotin modified nucleotides for introduction into a polynucleotide. The biotin then serves as the site for binding to avidin or antibodies, which may be labeled with a wide variety of labels, such as radionuclides, fluorescers, enzymes, or the like. Alternatively, antibodies may be employed which can recognize specific duplexes, including DNA duplexes, RNA duplexes, DNA-RNA hybrid duplexes, or

DNA-protein duplexes. The antibodies in turn may be labeled and the assay carried out where the duplex is bound to a surface, so that upon the formation of duplex on the surface, the presence of antibody bound to the duplex can be detected. The use of probes to the novel anti-sense RNA may be carried out in conventional techniques such as nucleic acid hybridization, plus and minus screening, recombinational probing, hybrid released translation (HRT), and hybrid arrested translation (HART). This also includes amplification techniques such as polymerase chain reaction (PCR).

Diagnostic kits which also test for the qualitative or quantitative presence of other markers are also contemplated. Diagnosis or prognosis may depend on the combination of multiple indications used as markers. Thus, kits may test for combinations of markers. See, e.g., Viallet, et al. (1989) Progress in Growth Factor Res. 1:89-97.

VIII. Therapeutic Utility

This invention provides reagents with significant therapeutic value. See, e.g., Levitzki (1996) Curr. Opin. Cell Biol. 8:239-244. The cytokine receptors (naturally occurring or recombinant), fragments thereof, mutein receptors, and antibodies, along with compounds identified as having binding affinity to the receptors or antibodies, should be useful in the treatment of conditions exhibiting abnormal expression of the receptors of their ligands. Such abnormality will typically be manifested by immunological disorders. Additionally, this invention should provide therapeutic value in various diseases or disorders associated with abnormal expression or abnormal triggering of response to the ligand. For example, the IL-1 ligands have been suggested to be involved in morphologic development, e.g., dorso-ventral polarity determination, and immune responses, particularly the primitive innate responses. See, e.g., Sun, et al. (1991) Eur. J. Biochem. 196:247-254; and Hultmark (1994) Nature 367:116-117.

Recombinant cytokine receptors, muteins, agonist or antagonist antibodies thereto, or antibodies can be purified and

then administered to a patient. These reagents can be combined for therapeutic use with additional active ingredients, e.g., in conventional pharmaceutically acceptable carriers or diluents, along with physiologically innocuous stabilizers and excipients. These combinations can be sterile, e.g., filtered, and placed into dosage forms as by lyophilization in dosage vials or storage in stabilized aqueous preparations. This invention also contemplates use of antibodies or binding fragments thereof which are not complement binding.

Ligand screening using cytokine receptor or fragments thereof can be performed to identify molecules having binding affinity to the receptors. Subsequent biological assays can then be utilized to determine if a putative ligand can provide competitive binding, which can block intrinsic stimulating activity. Receptor fragments can be used as a blocker or antagonist in that it blocks the activity of ligand. Likewise, a compound having intrinsic stimulating activity can activate the receptor and is thus an agonist in that it simulates the activity of ligand, e.g., inducing signaling. This invention further contemplates the therapeutic use of antibodies to cytokine receptors as antagonists.

The quantities of reagents necessary for effective therapy will depend upon many different factors, including means of administration, target site, reagent physiological life, pharmacological life, physiological state of the patient, and other medicants administered. Thus, treatment dosages should be titrated to optimize safety and efficacy. Typically, dosages used in vitro may provide useful guidance in the amounts useful for in situ administration of these reagents. Animal testing of effective doses for treatment of particular disorders will provide further predictive indication of human dosage. Various considerations are described, e.g., in Gilman, et al. (eds. 1990) Goodman and Gilman's: The Pharmacological Bases of Therapeutics, 8th Ed., Pergamon Press; and Remington's Pharmaceutical Sciences, 17th ed. (1990), Mack Publishing Co., Easton, Penn.; each of which is hereby incorporated herein by reference. Methods for administration are discussed therein and

below, e.g., for oral, intravenous, intraperitoneal, or intramuscular administration, transdermal diffusion, and others. Pharmaceutically acceptable carriers will include water, saline, buffers, and other compounds described, e.g., in the Merck Index, Merck & Co., Rahway, New Jersey. Because of the likely high affinity binding, or turnover numbers, between a putative ligand and its receptors, low dosages of these reagents would be initially expected to be effective. And the signaling pathway suggests extremely low amounts of ligand may have effect. Thus, dosage ranges would ordinarily be expected to be in amounts lower than 1 mM concentrations, typically less than about 10 μM concentrations, usually less than about 100 nM, preferably less than about 10 pM (picomolar), and most preferably less than about 1 fM (femtomolar), with an appropriate carrier. Slow release formulations, or slow release apparatus will often be utilized for continuous administration.

Cytokine receptors, fragments thereof, and antibodies or its fragments, antagonists, and agonists, may be administered directly to the host to be treated or, depending on the size of the compounds, it may be desirable to conjugate them to carrier proteins such as ovalbumin or serum albumin prior to their administration. Therapeutic formulations may be administered in many conventional dosage formulations. While it is possible for the active ingredient to be administered alone, it is preferable to present it as a pharmaceutical formulation. Formulations comprise at least one active ingredient, as defined above, together with one or more acceptable carriers thereof. Each carrier must be both pharmaceutically and physiologically acceptable in the sense of being compatible with the other ingredients and not injurious to the patient. Formulations include those suitable for oral, rectal, nasal, or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration. The formulations may conveniently be presented in unit dosage form and may be prepared by methods well known in the art of pharmacy. See, e.g., Gilman, et al. (eds. 1990) Goodman and Gilman's: The Pharmacological Bases of Therapeutics, 8th Ed., Pergamon Press; and Remington's

Pharmaceutical Sciences, 17th ed. (1990), Mack Publishing Co., Easton, Penn.; Avis, et al. (eds. 1993) Pharmaceutical Dosage Forms: Parenteral Medications Dekker, NY; Lieberman, et al. (eds. 1990) Pharmaceutical Dosage Forms: Tablets Dekker, NY; and Lieberman, et al. (eds. 1990) Pharmaceutical Dosage Forms: Disperse Systems Dekker, NY. The therapy of this invention may be combined with or used in association with other therapeutic agents, particularly agonists or antagonists of other cytokine receptor family members.

IX. Screening

Drug screening using DCRS3 or DCRS4 or fragments thereof can be performed to identify compounds having binding affinity to the receptor subunit, including isolation of associated components. Subsequent biological assays can then be utilized to determine if the compound has intrinsic stimulating activity and is therefore a blocker or antagonist in that it blocks the activity of the ligand. Likewise, a compound having intrinsic stimulating activity can activate the receptor and is thus an agonist in that it simulates the activity of a cytokine ligand. This invention further contemplates the therapeutic use of antibodies to the receptor as cytokine agonists or antagonists.

Similarly, complexes comprising multiple proteins may be used to screen for ligands or reagents capable of recognizing the complex. Most cytokine receptors comprise at least two subunits, which may be the same, or distinct. Alternatively, the transmembrane receptor may bind to a complex comprising a cytokine-like ligand associated with another soluble protein serving, e.g., as a second receptor subunit.

One method of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant DNA molecules expressing, e.g., a DCRS3 in combination with another cytokine receptor subunit. Cells may be isolated which express a receptor in isolation from other functional receptors. Such cells, either in viable or fixed form, can be used for standard antibody/antigen or ligand/receptor binding assays. See also, Parce, et al. (1989) Science 246:243-247; and Owicki, et al. (1990) Proc. Nat'l Acad.

Sci. USA 87:4007-4011, which describe sensitive methods to detect cellular responses. Competitive assays are particularly useful, where the cells (source of putative ligand) are contacted and incubated with a labeled receptor or antibody having known binding affinity to the ligand, such as ^{125}I-antibody, and a test sample whose binding affinity to the binding composition is being measured. The bound and free labeled binding compositions are then separated to assess the degree of ligand binding. The amount of test compound bound is inversely proportional to the amount of labeled receptor binding to the known source. Many techniques can be used to separate bound from free ligand to assess the degree of ligand binding. This separation step could typically involve a procedure such as adhesion to filters followed by washing, adhesion to plastic followed by washing, or centrifugation of the cell membranes. Viable cells could also be used to screen for the effects of drugs on cytokine mediated functions, e.g., second messenger levels, i.e., Ca^{++}; cell proliferation; inositol phosphate pool changes; and others. Some detection methods allow for elimination of a separation step, e.g., a proximity sensitive detection system. Calcium sensitive dyes will be useful for detecting Ca^{++} levels, with a fluorimeter or a fluorescence cell sorting apparatus.

X. Ligands

The descriptions of DCRS3 or DCRS4 herein provide means to identify ligands, as described above. Such ligand should bind specifically to the respective receptor with reasonably high affinity. Various constructs are made available which allow either labeling of the receptor to detect its ligand. For example, directly labeling cytokine receptor, fusing onto it markers for secondary labeling, e.g., FLAG or other epitope tags, etc., will allow detection of receptor. This can be histological, as an affinity method for biochemical purification, or labeling or selection in an expression cloning approach. A two-hybrid selection system may also be applied making appropriate constructs with the available cytokine

receptor sequences. See, e.g., Fields and Song (1989) Nature 340:245-246.

The broad scope of this invention is best understood with reference to the following examples, which are not intended to limit the inventions to the specific embodiments.

EXAMPLES

I. General Methods

Some of the standard methods are described or referenced, e.g., in Maniatis, et al. (1982) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Laboratory, Cold Spring Harbor Press; Sambrook, et al. (1989) Molecular Cloning: A Laboratory Manual, (2d ed.), vols. 1-3, CSH Press, NY; or Ausubel, et al. (1987 and Supplements) Current Protocols in Molecular Biology, Greene/Wiley, New York. Methods for protein purification include such methods as ammonium sulfate precipitation, column chromatography, electrophoresis, centrifugation, crystallization, and others. See, e.g., Ausubel, et al. (1987 and periodic supplements); Coligan, et al. (ed. 1996) and periodic supplements, Current Protocols In Protein Science Greene/Wiley, New York; Deutscher (1990) "Guide to Protein Purification" in Methods in Enzymology, vol. 182, and other volumes in this series; and manufacturer's literature on use of protein purification products, e.g., Pharmacia, Piscataway, N.J., or Bio-Rad, Richmond, CA. Combination with recombinant techniques allow fusion to appropriate segments, e.g., to a FLAG sequence or an equivalent which can be fused via a protease-removable sequence. See, e.g., Hochuli (1990) "Purification of Recombinant Proteins with Metal Chelate Absorbent" in Setlow (ed.) Genetic Engineering, Principle and Methods 12:87-98, Plenum Press, N.Y.; and Crowe, et al. (1992) QIAexpress: The High Level Expression & Protein Purification System QUIAGEN, Inc., Chatsworth, CA.

Computer sequence analysis is performed, e.g., using available software programs, including those from the GCG (U. Wisconsin) and GenBank sources. Public sequence databases were also used, e.g., from GenBank and others.

Many techniques applicable to IL-10 receptors may be applied to DCRS3 or DCRS4, as described, e.g., in USSN 08/110,683 (IL-10 receptor), which is incorporated herein by reference.

II. Computational Analysis

Human sequences related to cytokine receptors were identified from genomic sequence database using, e.g., the BLAST server (Altschul, et al. (1994) Nature Genet. 6:119-129). Standard analysis programs may be used to evaluate structure, e.g., PHD (Rost and Sander (1994) Proteins 19:55-72) and DSC (King and Sternberg (1996) Protein Sci. 5:2298-2310). Standard comparison software includes, e.g., Altschul, et al. (1990) J. Mol. Biol. 215:403-10; Waterman (1995) Introduction to Computational Biology: Maps, Sequences, and Genomes Chapman & Hall; Lander and Waterman (eds. 1995) Calculating the Secrets of Life: Applications of the Mathematical Sciences in Molecular Biology National Academy Press; and Speed and Waterman (eds. 1996) Genetic Mapping and DNA Sequencing (IMA Volumes in Mathematics and Its Applications, Vol 81) Springer Verlag.

III. Cloning of full-length DCRS3 or DCRS4 cDNAs; Chromosomal localization

PCR primers derived from DCRS3 or DCRS4 sequence are used to probe a human cDNA library. Sequences may be derived, e.g., from Table 1 or 3, preferably those adjacent the ends of sequences. Full length cDNAs for primate, rodent, or other species are cloned, e.g., by DNA hybridization screening of λgt10 phage. PCR reactions are conducted using T. aquaticus Taqplus DNA polymerase (Stratagene) under appropriate conditions.

For experimental confirmation of localization, chromosome spreads are prepared. In situ hybridization is performed on chromosome preparations obtained from phytohemagglutinin-stimulated human lymphocytes cultured for 72 h. 5-bromodeoxyuridine was added for the final seven hours of culture (60 μg/ml of medium), to ensure a posthybridization chromosomal banding of good quality.

A PCR fragment, amplified with the help of primers, is cloned into an appropriate vector. The vector is labeled by nick-translation with ^3H. The radiolabeled probe is hybridized to metaphase spreads at final concentration of 200 ng/ml of

hybridization solution as described in Mattei, et al. (1985) Hum. Genet. 69:327-331.

After coating with nuclear track emulsion (KODAK NTB_2), slides are exposed. To avoid any slipping of silver grains during the banding procedure, chromosome spreads are first stained with buffered Giemsa solution and metaphase photographed. R-banding is then performed by the fluorochrome-photolysis-Giemsa (FPG) method and metaphases rephotographed before analysis.

Similar appropriate methods are used for other species.

IV. Localization of DCRS mRNA

Human multiple tissue (Cat# 1, 2) and cancer cell line blots (Cat# 7757-1), containing approximately 2 µg of poly(A)$^+$ RNA per lane, are purchased from Clontech (Palo Alto, CA). Probes are radiolabeled with [α-^{32}P] dATP, e.g., using the Amersham Rediprime random primer labeling kit (RPN1633). Prehybridization and hybridizations are performed, e.g., at 65° C in 0.5 M Na_2HPO_4, 7% SDS, 0.5 M EDTA (pH 8.0). High stringency washes are conducted, e.g., at 65° C with two initial washes in 2 x SSC, 0.1% SDS for 40 min followed by a subsequent wash in 0.1 x SSC, 0.1% SDS for 20 min. Membranes are then exposed at -70° C to X-Ray film (Kodak) in the presence of intensifying screens. More detailed studies by cDNA library Southerns are performed with selected appropriate human DCRS3 clones to examine their expression in hemopoietic or other cell subsets.

Alternatively, two appropriate primers are selected from Tables 1 or 3. RT-PCR is used on an appropriate mRNA sample selected for the presence of message to produce a cDNA, e.g., a sample which expresses the gene.

Full length clones may be isolated by hybridization of cDNA libraries from appropriate tissues pre-selected by PCR signal. Northern blots can be performed.

Message for genes encoding DCRS3 or DCRS4 will be assayed by appropriate technology, e.g., PCR, immunoassay, hybridization, or otherwise. Tissue and organ cDNA preparations

are available, e.g., from Clontech, Mountain View, CA. Identification of sources of natural expression are useful, as described. And the identification of functional receptor subunit pairings will allow for prediction of what cells express the combination of receptor subunits which will result in a physiological responsiveness to each of the cytokine ligands.

For mouse distribution, e.g., Southern Analysis can be performed: DNA (5 μg) from a primary amplified cDNA library was digested with appropriate restriction enzymes to release the inserts, run on a 1% agarose gel and transferred to a nylon membrane (Schleicher and Schuell, Keene, NH).

Samples for mouse mRNA isolation may include: resting mouse fibroblastic L cell line (C200); Braf:ER (Braf fusion to estrogen receptor) transfected cells, control (C201); T cells, TH1 polarized (Mel14 bright, CD4+ cells from spleen, polarized for 7 days with IFN-γ and anti IL-4; T200); T cells, TH2 polarized (Mel14 bright, CD4+ cells from spleen, polarized for 7 days with IL-4 and anti-IFN-γ; T201); T cells, highly TH1 polarized (see Openshaw, et al. (1995) J. Exp. Med. 182:1357-1367; activated with anti-CD3 for 2, 6, 16 h pooled; T202); T cells, highly TH2 polarized (see Openshaw, et al. (1995) J. Exp. Med. 182:1357-1367; activated with anti-CD3 for 2, 6, 16 h pooled; T203); CD44- CD25+ pre T cells, sorted from thymus (T204); TH1 T cell clone D1.1, resting for 3 weeks after last stimulation with antigen (T205); TH1 T cell clone D1.1, 10 μg/ml ConA stimulated 15 h (T206); TH2 T cell clone CDC35, resting for 3 weeks after last stimulation with antigen (T207); TH2 T cell clone CDC35, 10 μg/ml ConA stimulated 15 h (T208); Mel14+ naive T cells from spleen, resting (T209); Mel14+ T cells, polarized to Th1 with IFN-γ/IL-12/anti-IL-4 for 6, 12, 24 h pooled (T210); Mel14+ T cells, polarized to Th2 with IL-4/anti-IFN-γ for 6, 13, 24 h pooled (T211); unstimulated mature B cell leukemia cell line A20 (B200); unstimulated B cell line CH12 (B201); unstimulated large B cells from spleen (B202); B cells from total spleen, LPS activated (B203); metrizamide enriched dendritic cells from spleen, resting (D200); dendritic cells from bone marrow, resting (D201); monocyte cell line RAW 264.7

activated with LPS 4 h (M200); bone-marrow macrophages derived with GM and M-CSF (M201); macrophage cell line J774, resting (M202); macrophage cell line J774 + LPS + anti-IL-10 at 0.5, 1, 3, 6, 12 h pooled (M203); macrophage cell line J774 + LPS + IL-10 at 0.5, 1, 3, 5, 12 h pooled(M204); aerosol challenged mouse lung tissue, Th2 primers, aerosol OVA challenge 7, 14, 23 h pooled (see Garlisi, et al. (1995) Clinical Immunology and Immunopathology 75:75-83; X206); Nippostrongulus-infected lung tissue (see Coffman, et al. (1989) Science 245:308-310; X200); total adult lung, normal (O200); total lung, rag-1 (see Schwarz, et al. (1993) Immunodeficiency 4:249-252; O205); IL-10 K.O. spleen (see Kuhn, et al. (1991) Cell 75:263-274; X201); total adult spleen, normal (O201); total spleen, rag-1 (O207); IL-10 K.O. Peyer's patches (O202); total Peyer's patches, normal (O210); IL-10 K.O. mesenteric lymph nodes (X203); total mesenteric lymph nodes, normal (O211); IL-10 K.O. colon (X203); total colon, normal (O212); NOD mouse pancreas (see Makino, et al. (1980) Jikken Dobutsu 29:1-13; X205); total thymus, rag-1 (O208); total kidney, rag-1 (O209); total heart, rag-1 (O202); total brain, rag-1 (O203); total testes, rag-1 (O204); total liver, rag-1 (O206); rat normal joint tissue (O300); and rat arthritic joint tissue (X300).

Samples for human mRNA isolation may include: peripheral blood mononuclear cells (monocytes, T cells, NK cells, granulocytes, B cells), resting (T100); peripheral blood mononuclear cells, activated with anti-CD3 for 2, 6, 12 h pooled (T101); T cell, TH0 clone Mot 72, resting (T102); T cell, TH0 clone Mot 72, activated with anti-CD28 and anti-CD3 for 3, 6, 12 h pooled (T103); T cell, TH0 clone Mot 72, anergic treated with specific peptide for 2, 7, 12 h pooled (T104); T cell, TH1 clone HY06, resting (T107); T cell, TH1 clone HY06, activated with anti-CD28 and anti-CD3 for 3, 6, 12 h pooled (T108); T cell, TH1 clone HY06, anergic treated with specific peptide for 2, 6, 12 h pooled (T109); T cell, TH2 clone HY935, resting (T110); T cell, TH2 clone HY935, activated with anti-CD28 and anti-CD3 for 2, 7, 12 h pooled (T111); T cells CD4+CD45RO- T cells polarized 27 days in anti-CD28, IL-4, and anti IFN-γ, TH2 polarized, activated

with anti-CD3 and anti-CD28 4 h (T116); T cell tumor lines Jurkat and Hut78, resting (T117); T cell clones, pooled AD130.2, Tc783.12, Tc783.13, Tc783.58, Tc782.69, resting (T118); T cell random γδ T cell clones, resting (T119); Splenocytes, resting (B100); Splenocytes, activated with anti-CD40 and IL-4 (B101); B cell EBV lines pooled WT49, RSB, JY, CVIR, 721.221, RM3, HSY, resting (B102); B cell line JY, activated with PMA and ionomycin for 1, 6 h pooled (B103); NK 20 clones pooled, resting (K100); NK 20 clones pooled, activated with PMA and ionomycin for 6 h (K101); NKL clone, derived from peripheral blood of LGL leukemia patient, IL-2 treated (K106); NK cytotoxic clone 640-A30-1, resting (K107); hematopoietic precursor line TF1, activated with PMA and ionomycin for 1, 6 h pooled (C100); U937 premonocytic line, resting (M100); U937 premonocytic line, activated with PMA and ionomycin for 1, 6 h pooled (M101); elutriated monocytes, activated with LPS, IFNγ, anti-IL-10 for 1, 2, 6, 12, 24 h pooled (M102); elutriated monocytes, activated with LPS, IFNγ, IL-10 for 1, 2, 6, 12, 24 h pooled (M103); elutriated monocytes, activated with LPS, IFNγ, anti-IL-10 for 4, 16 h pooled (M106); elutriated monocytes, activated with LPS, IFNγ, IL-10 for 4, 16 h pooled (M107); elutriated monocytes, activated LPS for 1 h (M108); elutriated monocytes, activated LPS for 6 h (M109); DC 70% CD1a+, from CD34+ GM-CSF, TNFα 12 days, resting (D101); DC 70% CD1a+, from CD34+ GM-CSF, TNFα 12 days, activated with PMA and ionomycin for 1 hr (D102); DC 70% CD1a+, from CD34+ GM-CSF, TNFα 12 days, activated with PMA and ionomycin for 6 hr (D103); DC 95% CD1a+, from CD34+ GM-CSF, TNFα 12 days FACS sorted, activated with PMA and ionomycin for 1, 6 h pooled (D104); DC 95% CD14+, ex CD34+ GM-CSF, TNFα 12 days FACS sorted, activated with PMA and ionomycin 1, 6 hr pooled (D105); DC CD1a+ CD86+, from CD34+ GM-CSF, TNFα 12 days FACS sorted, activated with PMA and ionomycin for 1, 6 h pooled (D106); DC from monocytes GM-CSF, IL-4 5 days, resting (D107); DC from monocytes GM-CSF, IL-4 5 days, resting (D108); DC from monocytes GM-CSF, IL-4 5 days, activated LPS 4, 16 h pooled (D109); DC from monocytes GM-CSF, IL-4 5 days, activated TNFα, monocyte supe for 4, 16 h pooled (D110); leiomyoma L11 benign tumor (X101); normal myometrium M5

(O115); malignant leiomyosarcoma GS1 (X103); lung fibroblast sarcoma line MRC5, activated with PMA and ionomycin for 1, 6 h pooled (C101); kidney epithelial carcinoma cell line CHA, activated with PMA and ionomycin for 1, 6 h pooled (C102); kidney fetal 28 wk male (O100); lung fetal 28 wk male (O101); liver fetal 28 wk male (O102); heart fetal 28 wk male (O103); brain fetal 28 wk male (O104); gallbladder fetal 28 wk male (O106); small intestine fetal 28 wk male (O107); adipose tissue fetal 28 wk male (O108); ovary fetal 25 wk female (O109); uterus fetal 25 wk female (O110); testes fetal 28 wk male (O111); spleen fetal 28 wk male (O112); adult placenta 28 wk (O113); and tonsil inflamed, from 12 year old (X100).

Similar samples may isolated in other species for evaluation.

V. Cloning of species counterparts of DCRS3 or DCRS4

Various strategies are used to obtain species counterparts of DCRS3 or DCRS4, preferably from other primates or rodents. One method is by cross hybridization using closely related species DNA probes. It may be useful to go into evolutionarily similar species as intermediate steps. Another method is by using specific PCR primers based on the identification of blocks of similarity or difference between genes, e.g., areas of highly conserved or nonconserved polypeptide or nucleotide sequence. Antibody based screening methods are also available, e.g., in expression cloning.

VI. Production of mammalian DCRS3 or DCRS4 protein

An appropriate, e.g., GST, fusion construct is engineered for expression, e.g., in E. coli. For example, a mouse IGIF pGex plasmid is constructed and transformed into E. coli. Freshly transformed cells are grown, e.g., in LB medium containing 50 µg/ml ampicillin and induced with IPTG (Sigma, St. Louis, MO). After overnight induction, the bacteria are harvested and the pellets containing, e.g., DCRS3, protein are isolated. The pellets are homogenized, e.g., in TE buffer (50 mM Tris-base pH 8.0, 10 mM EDTA and 2 mM pefabloc) in 2 liters.

This material is passed through a microfluidizer (Microfluidics, Newton, MA) three times. The fluidized supernatant is spun down on a Sorvall GS-3 rotor for 1 h at 13,000 rpm. The resulting supernatant containing the cytokine receptor protein is filtered and passed over a glutathione-SEPHAROSE column equilibrated in 50 mM Tris-base pH 8.0. The fractions containing the DCRS3-GST fusion protein are pooled and cleaved, e.g., with thrombin (Enzyme Research Laboratories, Inc., South Bend, IN). The cleaved pool is then passed over a Q-SEPHAROSE column equilibrated in 50 mM Tris-base. Fractions containing DCRS3 are pooled and diluted in cold distilled H_2O, to lower the conductivity, and passed back over a fresh Q-Sepharose column, alone or in succession with an immunoaffinity antibody column. Fractions containing DCRS3 protein are pooled, aliquoted, and stored in the -70° C freezer.

Comparison of the CD spectrum with cytokine receptor protein may suggest that the protein is correctly folded. See Hazuda, et al. (1969) J. Biol. Chem. 264:1689-1693.

VII. Preparation of antibodies specific for DCRS3 or DCRS4

Inbred Balb/c mice are immunized intraperitoneally with recombinant forms of the protein, e.g., purified DCRS3 or stable transfected NIH-3T3 cells. Animals are boosted at appropriate time points with protein, with or without additional adjuvant, to further stimulate antibody production. Serum is collected, or hybridomas produced with harvested spleens.

Alternatively, Balb/c mice are immunized with cells transformed with the gene or fragments thereof, either endogenous or exogenous cells, or with isolated membranes enriched for expression of the antigen. Serum is collected at the appropriate time, typically after numerous further administrations. Various gene therapy techniques may be useful, e.g., in producing protein in situ, for generating an immune response. Serum or antibody preparations may be cross-absorbed or immunoselected to prepare substantially purified antibodies of defined specificity and high affinity.

Monoclonal antibodies may be made. For example, splenocytes are fused with an appropriate fusion partner and hybridomas are selected in growth medium by standard procedures. Hybridoma supernatants are screened for the presence of antibodies which bind to DCRS3, e.g., by ELISA or other assay. Antibodies which specifically recognize specific DCRS3 embodiments may also be selected or prepared.

In another method, synthetic peptides or purified protein are presented to an immune system to generate monoclonal or polyclonal antibodies. See, e.g., Coligan (ed. 1991) Current Protocols in Immunology Wiley/Greene; and Harlow and Lane (1989) Antibodies: A Laboratory Manual Cold Spring Harbor Press. In appropriate situations, the binding reagent is either labeled as described above, e.g., fluorescence or otherwise, or immobilized to a substrate for panning methods. Nucleic acids may also be introduced into cells in an animal to produce the antigen, which serves to elicit an immune response. See, e.g., Wang, et al. (1993) Proc. Nat'l. Acad. Sci. 90:4156-4160; Barry, et al. (1994) BioTechniques 16:616-619; and Xiang, et al. (1995) Immunity 2: 129-135.

VIII. Production of fusion proteins with DCRS

Various fusion constructs are made with DCRS. A portion of the appropriate gene is fused to an epitope tag, e.g., a FLAG tag, or to a two hybrid system construct. See, e.g., Fields and Song (1989) Nature 340:245-246.

The epitope tag may be used in an expression cloning procedure with detection with anti-FLAG antibodies to detect a binding partner, e.g., ligand for the respective cytokine receptor. The two hybrid system may also be used to isolate proteins which specifically bind to DCRS.

IX. Structure activity relationship

Information on the criticality of particular residues is determined using standard procedures and analysis. Standard mutagenesis analysis is performed, e.g., by generating many different variants at determined positions, e.g., at the

positions identified above, and evaluating biological activities of the variants. This may be performed to the extent of determining positions which modify activity, or to focus on specific positions to determine the residues which can be substituted to either retain, block, or modulate biological activity.

Alternatively, analysis of natural variants can indicate what positions tolerate natural mutations. This may result from populational analysis of variation among individuals, or across strains or species. Samples from selected individuals are analyzed, e.g., by PCR analysis and sequencing. This allows evaluation of population polymorphisms.

X. Isolation of a ligand for DCRS

A cytokine receptor can be used as a specific binding reagent to identify its binding partner, by taking advantage of its specificity of binding, much like an antibody would be used. The binding receptor may be a heterodimer of receptor subunits; or may involve, e.g., a complex of the DCRS with another subunit. A binding reagent is either labeled as described above, e.g., fluorescence or otherwise, or immobilized to a substrate for panning methods.

The binding composition is used to screen an expression library made from a cell line which expresses a binding partner, i.e., ligand, preferably membrane associated. Standard staining techniques are used to detect or sort surface expressed ligand, or surface expressing transformed cells are screened by panning. Screening of intracellular expression is performed by various staining or immunofluorescence procedures. See also McMahan, et al. (1991) EMBO J. 10:2821-2832.

For example, on day 0, precoat 2-chamber permanox slides with 1 ml per chamber of fibronectin, 10 ng/ml in PBS, for 30 min at room temperature. Rinse once with PBS. Then plate COS cells at 2-3 x 10^5 cells per chamber in 1.5 ml of growth media. Incubate overnight at 37°C.

On day 1 for each sample, prepare 0.5 ml of a solution of 66 µg/ml DEAE-dextran, 66 µM chloroquine, and 4 µg DNA in serum

free DME. For each set, a positive control is prepared, e.g., of DCRS-FLAG cDNA at 1 and 1/200 dilution, and a negative mock. Rinse cells with serum free DME. Add the DNA solution and incubate 5 hr at 37°C. Remove the medium and add 0.5 ml 10% DMSO in DME for 2.5 min. Remove and wash once with DME. Add 1.5 ml growth medium and incubate overnight.

On day 2, change the medium. On days 3 or 4, the cells are fixed and stained. Rinse the cells twice with Hank's Buffered Saline Solution (HBSS) and fix in 4% paraformaldehyde (PFA)/glucose for 5 min. Wash 3X with HBSS. The slides may be stored at -80°C after all liquid is removed. For each chamber, 0.5 ml incubations are performed as follows. Add HBSS/saponin (0.1%) with 32 µl/ml of 1 M NaN_3 for 20 min. Cells are then washed with HBSS/saponin 1X. Add appropriate DCRS or DCRS/antibody complex to cells and incubate for 30 min. Wash cells twice with HBSS/saponin. If appropriate, add first antibody for 30 min. Add second antibody, e.g., Vector anti-mouse antibody, at 1/200 dilution, and incubate for 30 min. Prepare ELISA solution, e.g., Vector Elite ABC horseradish peroxidase solution, and preincubate for 30 min. Use, e.g., 1 drop of solution A (avidin) and 1 drop solution B (biotin) per 2.5 ml HBSS/saponin. Wash cells twice with HBSS/saponin. Add ABC HRP solution and incubate for 30 min. Wash cells twice with HBSS, second wash for 2 min, which closes cells. Then add Vector diaminobenzoic acid (DAB) for 5 to 10 min. Use 2 drops of buffer plus 4 drops DAB plus 2 drops of H_2O_2 per 5 ml of glass distilled water. Carefully remove chamber and rinse slide in water. Air dry for a few minutes, then add 1 drop of Crystal Mount and a cover slip. Bake for 5 min at 85-90°C.

Evaluate positive staining of pools and progressively subclone to isolation of single genes responsible for the binding.

Alternatively, receptor reagents are used to affinity purify or sort out cells expressing a putative ligand. See, e.g., Sambrook, et al. or Ausubel, et al.

Another strategy is to screen for a membrane bound receptor by panning. The receptor cDNA is constructed as described

above. Immobilization may be achieved by use of appropriate antibodies which recognize, e.g., a FLAG sequence of a DCRS fusion construct, or by use of antibodies raised against the first antibodies. Recursive cycles of selection and amplification lead to enrichment of appropriate clones and eventual isolation of receptor expressing clones.

Phage expression libraries can be screened by mammalian DCRS. Appropriate label techniques, e.g., anti-FLAG antibodies, will allow specific labeling of appropriate clones.

All citations herein are incorporated herein by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

Many modifications and variations of this invention can be made without departing from its spirit and scope, as will be apparent to those skilled in the art. The specific embodiments described herein are offered by way of example only, and the invention is to be limited by the terms of the appended claims, along with the full scope of equivalents to which such claims are entitled; and the invention is not to be limited by the specific embodiments that have been presented herein by way of example.

WHAT IS CLAIMED IS:

1. A composition of matter selected from:

a) a substantially pure or recombinant DCRS3 polypeptide comprising at least three distinct nonoverlapping segments of at least four amino acids identical to segments of SEQ ID NO: 2 or 25;

b) a substantially pure or recombinant DCRS3 polypeptide comprising at least two distinct nonoverlapping segments of at least five amino acids identical to segments of SEQ ID NO: 2 or 25;

c) a natural sequence DCRS3 comprising mature SEQ ID NO: 2 or 25;

d) a fusion polypeptide comprising DCRS3 sequence;

e) a substantially pure or recombinant DCRS4 polypeptide comprising at least three distinct nonoverlapping segments of at least four amino acids identical to segments of SEQ ID NO: 5, 28, or 31;

f) a substantially pure or recombinant DCRS4 polypeptide comprising at least two distinct nonoverlapping segments of at least five amino acids identical to segments of SEQ ID NO: 5, 28, or 31;

g) a natural sequence DCRS4 comprising mature SEQ ID NO: 5, 28, or 31; or

h) a fusion polypeptide comprising DCRS4 sequence.

2. The substantially pure or isolated antigenic DCRS3 or DCRS4 polypeptide of Claim 1, wherein said distinct nonoverlapping segments of identity:

a) include one of at least eight amino acids;

b) include one of at least four amino acids and a second of at least five amino acids;

c) include at least three segments of at least four, five, and six amino acids, or

d) include one of at least twelve amino acids.

3. The composition of matter of Claim 1, wherein said:

a) DCRS3 polypeptide:

i) comprises a mature sequence of Table 1;
ii) is an unglycosylated form of DCRS3;
iii) is from a primate, such as a human;
iv) comprises at least seventeen amino acids of SEQ ID NO: 2 or 25;
v) exhibits at least four nonoverlapping segments of at least seven amino acids of SEQ ID NO: 2 or 25;
vi) comprises a sequence of at least 3 amino acids on each side across an exon boundary;
vii) is a natural allelic variant of DCRS3;
viii) has a length at least about 30 amino acids;
ix) exhibits at least two non-overlapping epitopes which are specific for a primate DCRS3;
x) is glycosylated;
xi) has a molecular weight of at least 30 kD with natural glycosylation;
xii) is a synthetic polypeptide;
xiii) is attached to a solid substrate;
xiv) is conjugated to another chemical moiety;
xv) is a 5-fold or less substitution from natural sequence; or
xvi) is a deletion or insertion variant from a natural sequence; or

b) DCRS4 polypeptide:
i) comprises a mature sequence of Table 3;
ii) is an unglycosylated form of DCRS4;
iii) is from a primate, such as a human;
iv) comprises at least seventeen amino acids of SEQ ID NO: 5, 28, or 31;
v) exhibits at least four nonoverlapping segments of at least seven amino acids of SEQ ID NO: 5, 28, or 31;
vi) comprises a sequence of at least 3 amino acids on each side across an exon boundary;
vii) is a natural allelic variant of DCRS4;
viii) has a length at least about 30 amino acids;

ix) exhibits at least two non-overlapping epitopes which are specific for a primate DCRS4;

x) is glycosylated;

xi) has a molecular weight of at least 30 kD with natural glycosylation;

xii) is a synthetic polypeptide;

xiii) is attached to a solid substrate;

xiv) is conjugated to another chemical moiety;

xv) is a 5-fold or less substitution from natural sequence; or

xvi) is a deletion or insertion variant from a natural sequence.

4. A composition comprising:

a) a substantially pure DCRS3 and another cytokine receptor family member;

b) a sterile DCRS3 polypeptide of Claim 1;

c) said DCRS3 polypeptide of Claim 1 and a carrier, wherein said carrier is:

i) an aqueous compound, including water, saline, and/or buffer; and/or

ii) formulated for oral, rectal, nasal, topical, or parenteral administration; or

d) a substantially pure DCRS4 and another cytokine receptor family member;

e) a sterile DCRS4 polypeptide of Claim 1;

f) said DCRS4 polypeptide of Claim 1 and a carrier, wherein said carrier is:

i) an aqueous compound, including water, saline, and/or buffer; and/or

ii) formulated for oral, rectal, nasal, topical, or parenteral administration.

5. The fusion polypeptide of Claim 1, comprising:

a) mature protein sequence of Table 1;

b) mature protein sequence of Table 1;

c) a detection or purification tag, including a FLAG, His6, or Ig sequence; or

d) sequence of another cytokine receptor protein.

6. A kit comprising a polypeptide of Claim 1, and:

a) a compartment comprising said protein or polypeptide; or

b) instructions for use or disposal of reagents in said kit.

7. A binding compound comprising an antigen binding site from an antibody, which specifically binds to a natural:

A) DCRS3 polypeptide of Claim 1, wherein:

a) said binding compound is in a container;

b) said polypeptide is from a human;

c) said binding compound is an Fv, Fab, or Fab2 fragment;

d) said binding compound is conjugated to another chemical moiety; or

e) said antibody:

i) is raised against a peptide sequence of a mature polypeptide of Table 1;

ii) is raised against a mature DCRS3;

iii) is raised to a purified human DCRS3;

iv) is immunoselected;

v) is a polyclonal antibody;

vi) binds to a denatured DCRS3;

vii) exhibits a Kd to antigen of at least 30 μM;

viii) is attached to a solid substrate, including a bead or plastic membrane;

ix) is in a sterile composition; or

x) is detectably labeled, including a radioactive or fluorescent label; or

B) DCRS4 polypeptide of Claim 1, wherein:

a) said binding compound is in a container;

b) said polypeptide is from a human;

c) said binding compound is an Fv, Fab, or Fab2 fragment;

d) said binding compound is conjugated to another chemical moiety; or

e) said antibody:

i) is raised against a peptide sequence of a mature polypeptide of Table 3;

ii) is raised against a mature DCRS4;

iii) is raised to a purified human DCRS4;

iv) is immunoselected;

v) is a polyclonal antibody;

vi) binds to a denatured DCRS4;

vii) exhibits a Kd to antigen of at least 30 μM;

viii) is attached to a solid substrate, including a bead or plastic membrane;

ix) is in a sterile composition; or

x) is detectably labeled, including a radioactive or fluorescent label.

8. A kit comprising said binding compound of Claim 7, and:

a) a compartment comprising said binding compound; or

b) instructions for use or disposal of reagents in said kit.

9. A method of producing an antigen:antibody complex, comprising contacting under appropriate conditions a primate:

a) DCRS3 polypeptide with an antibody of Claim 7, thereby allowing said complex to form; or

b) DCRS4 polypeptide with an antibody of Claim 7, thereby allowing said complex to form.

10. The method of Claim 9, wherein:

a) said complex is purified from other cytokine receptors;

b) said complex is purified from other antibody;

c) said contacting is with a sample comprising an interferon;

d) said contacting allows quantitative detection of said antigen;

e) said contacting is with a sample comprising said antibody; or

f) said contacting allows quantitative detection of said antibody.

11. A composition comprising:

a) a sterile binding compound of Claim 7, or

b) said binding compound of Claim 7 and a carrier, wherein said carrier is:

i) an aqueous compound, including water, saline, and/or buffer; and/or

ii) formulated for oral, rectal, nasal, topical, or parenteral administration.

12. An isolated or recombinant nucleic acid encoding said:

A) DCRS3 polypeptide of Claim 1, wherein said:

a) DCRS3 is from a human; or

b) said nucleic acid:

i) encodes an antigenic peptide sequence of Table 1;

ii) encodes a plurality of antigenic peptide sequences of Table 1;

iii) exhibits identity over at least thirteen nucleotides to a natural cDNA encoding said segment;

iv) is an expression vector;

v) further comprises an origin of replication;

vi) is from a natural source;

vii) comprises a detectable label;

viii) comprises synthetic nucleotide sequence;

ix) is less than 6 kb, preferably less than 3 kb;

x) is from a primate;

xi) comprises a natural full length coding sequence;

xii) is a hybridization probe for a gene encoding said DCRS3; or

xiii) is a PCR primer, PCR product, or mutagenesis primer; or

B) DCRS4 polypeptide of Claim 1, wherein said:

a) DCRS4 is from a human; or
b) said nucleic acid:
   i) encodes an antigenic peptide sequence of Table 3;
   ii) encodes a plurality of antigenic peptide sequences of Table 3;
   iii) exhibits identity over at least thirteen nucleotides to a natural cDNA encoding said segment;
   iv) is an expression vector;
   v) further comprises an origin of replication;
   vi) is from a natural source;
   vii) comprises a detectable label;
   viii) comprises synthetic nucleotide sequence;
   ix) is less than 6 kb, preferably less than 3 kb;
   x) is from a primate;
   xi) comprises a natural full length coding sequence;
   xii) is a hybridization probe for a gene encoding said DCRS4; or
   xiii) is a PCR primer, PCR product, or mutagenesis primer.

13. A cell or tissue comprising said recombinant nucleic acid of Claim 12.

14. The cell of Claim 13, wherein said cell is:
a) a prokaryotic cell;
b) a eukaryotic cell;
c) a bacterial cell;
d) a yeast cell;
e) an insect cell;
f) a mammalian cell;
g) a mouse cell;
h) a primate cell; or
i) a human cell.

15. A kit comprising said nucleic acid of Claim 12, and:
a) a compartment comprising said nucleic acid;

b) a compartment further comprising a primate DCRS3 or DCRS4 polypeptide; or

c) instructions for use or disposal of reagents in said kit.

16. A nucleic acid which:

a) hybridizes under wash conditions of 30 minutes at 30° C and less than 2M salt to the coding portion of SEQ ID NO: 1 or 24; or

b) exhibits identity over a stretch of at least about 30 nucleotides to a primate DCRS3;

a) hybridizes under wash conditions of 30 minutes at 30° C and less than 2M salt to the coding portion of SEQ ID NO: 4, 27, or 30; or

b) exhibits identity over a stretch of at least about 30 nucleotides to a primate DCRS4.

17. The nucleic acid of Claim 16, wherein:

a) said wash conditions are at 45° C and/or 500 mM salt; or

b) said stretch is at least 55 nucleotides.

18. The nucleic acid of Claim 16, wherein:

a) said wash conditions are at 55° C and/or 150 mM salt; or

b) said stretch is at least 75 nucleotides.

19. A method of modulating physiology or development of a cell or tissue culture cells comprising contacting said cell with an agonist or antagonist of a mammalian DCRS3 or DCRS4.

20. The method of Claim 19, wherein said cell is transformed with a nucleic acid encoding a DCRS3 or DCRS4 and another cytokine receptor subunit.

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125 130 135 140

Ser Arg Gln Tyr Asn Ile Ser Trp Arg Ser Asp Tyr Glu Asp Pro Ala
145 150 155

Phe Tyr Met Leu Lys Gly Lys Leu Gln Tyr Glu Leu Gln Tyr Arg Asn
160 165 170

Arg Gly Asp Pro Trp Ala Val Ser Pro Arg Arg Lys Leu Ile Ser Val
175 180 185

Asp Ser Arg Ser Val Ser Leu Leu Pro Leu Glu Phe Arg Lys Asp Ser
190 195 200

Ser Tyr Glu Leu Gln Val Arg Ala Gly Pro Met Pro Gly Ser Ser Tyr
205 210 215 220

Gln Gly Thr Trp Ser Glu Trp Ser Asp Pro Val Ile Phe Gln Thr Gln
225 230 235

Ser Glu Glu Leu Lys Glu Gly Trp Asn Pro His Leu Leu Leu Leu Leu
240 245 250

Leu Leu Val Ile Val Phe Ile Pro Ala Phe Trp Ser Leu Lys Thr His
255 260 265

Pro Leu Trp Arg Leu Trp Lys Lys Ile Trp Ala Val Pro Ser Pro Glu
270 275 280

Arg Phe Phe Met Pro Leu Tyr Lys Gly Cys Ser Gly Asp Phe Lys Lys
285 290 295 300

Trp Val Gly Ala Pro Phe Thr Gly Ser Ser Leu Glu Leu Gly Pro Trp
305 310 315

Ser Pro Glu Val Pro Ser Thr Leu Glu Val Tyr Ser Cys His Pro Pro
320 325 330

Arg Ser Pro Ala Lys Arg Leu Gln Leu Thr Glu Leu Gln Glu Pro Ala
335 340 345

Glu Leu Val Glu Ser Asp Gly Val Pro Lys Pro Ser Phe Trp Pro Thr
350 355 360

Ala Gln Asn Ser Gly Gly Ser Ala Tyr Ser Glu Glu Arg Asp Arg Pro
365 370 375 380

Tyr Gly Leu Val Ser Ile Asp Thr Val Thr Val Leu Asp Ala Glu Gly
385 390 395

Pro Cys Thr Trp Pro Cys Ser Cys Glu Asp Asp Gly Tyr Pro Ala Leu
400 405 410

Asp Leu Asp Ala Gly Leu Glu Pro Ser Pro Gly Leu Glu Asp Pro Leu
415 420 425

Leu Asp Ala Gly Thr Thr Val Leu Ser Cys Gly Cys Val Ser Ala Gly
430 435 440

Ser Pro Gly Leu Gly Gly Pro Leu Gly Ser Leu Leu Asp Arg Leu Lys
445 450 455 460

Pro Pro Leu Ala Asp Gly Glu Asp Trp Ala Gly Gly Leu Pro Trp Gly
465 470 475

Gly Arg Ser Pro Gly Gly Val Ser Glu Ser Glu Ala Gly Ser Pro Leu
480 485 490

Ala Gly Leu Asp Met Asp Thr Phe Asp Ser Gly Phe Val Gly Ser Asp
495 500 505

Cys Ser Ser Pro Val Glu Cys Asp Phe Thr Ser Pro Gly Asp Glu Gly
510 515 520

Pro Pro Arg Ser Tyr Leu Arg Gln Trp Val Val Ile Pro Pro Pro Leu
525 530 535 540

Ser Ser Pro Gly Pro Gln Ala Ser
545

<210> 3
<211> 1704
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:reverse translation

<220>
<221> misc_feature
<222> (6)..(1704)
<223> n may be a, c, g, or t

<400> 3
atgccnmgng gntgggcngc nccnytnytn ytnytnytny tncarggngc nytngarggn 60

atggarmgna arytntgyws nccnaarccn ccnccnacna argcnwsnyt nccnacngay 120

ccnccnggnt ggggntgycc ngayytngtn tgytayacng aytayytnca racngtnath 180

tgyathytng aratgtggaa yytncayccn wsnacnytna cnytnacntg gathytnwsn 240

aayaayacng gntgytayat haargaymgn acnytngayy tnmgncarga ycartaygar 300

garytnaarg aygargcnac nwsntgywsn ytncaymgnw sngcncayaa ygcnacncay 360

gcnacntaya cntgycayat ggaygtntty cayttyatgg cngaygayat httywsngtn 420

aayathacng aycarwsngg naaytaywsn cargartgyg gnwsnttyyt nytngcngar 480

wsnmgncart ayaayathws ntggmgnwsn gaytaygarg ayccngcntt ytayatgytn 540

aarggnaary tncartayga rytncartay mgnaaymgng gngayccntg ggcngtnwsn 600

ccnmgnmgna arytnathws ngtngaywsn mgnwsngtnw snytnytncc nytngartty 660

mgnaargayw snwsntayga rytncargtn mgngcnggnc cnatgccngg nwsnwsntay 720

carggnacnt ggwsngartg gwsngayccn gtnathttyc aracncarws ngargarytn 780

aargarggnt ggaayccnca yytnytnytn ytnytnytny tngtnathgt nttyathccn 840

gcnttytggw snytnaarac ncayccnytn tggmgnytnt ggaaraarat htgggcngtn 900

ccnwsnccng armgnttytt yatgccnytn tayaarggnt gywsnggnga yttyaaraar 960

tgggtnggng cnccnttyac nggnwsnwsn ytngarytng gnccntggws nccngargtn 1020

ccnwsnacny tngargtnta ywsntgycay ccnccnmgnw snccngcnaa rmgnytncar 1080

ytnacngary tncargarcc ngcngarytn gtngarwsng ayggngtncc naarccnwsn 1140

ttytggccna cngcncaraa ywsnggnggn wsngcntayw sngargarmg ngaymgnccn 1200

tayggnytng tnwsnathga yacngtnacn gtnytngayg cngarggncc ntgyacntgg 1260

ccntgywsnt gygargayga yggntayccn gcnytngayy tngaygcngg nytngarccn 1320

wsnccnggny tngargaycc nytnytngay gcnggnacna cngtnytnws ntgyggntgy 1380

gtnwsngcng gnwsnccngg nytnggnggn ccnytnggnw snytnytnga ymgnytnaar 1440

ccnccnytng cngayggnga rgaytgggcn ggnggnytnc cntggggngg nmgnwsnccn 1500

ggnggngtnw sngarwsnga rgcnggnwsn ccnytngcng gnytngayat ggayacntty 1560

gaywsnggnt tygtnggnws ngaytgywsn wsnccngtng artgygaytt yacnwsnccn 1620

ggngaygarg gnccnccnmg nwsntayytn mgncartggg tngtnathcc nccnccnytn 1680

wsnwsnccng gnccncargc nwsn 1704

<210> 4
<211> 750
<212> DNA
<213> primate; surmised Homo sapiens

<220>
<221> CDS
<222> (1)..(747)

<220>
<221> mat_peptide
<222> (64)..(747)

<400> 4
atg atg cct aaa cat tgc ttt cta ggc ttc ctc atc agt ttc ttc ctt 48
Met Met Pro Lys His Cys Phe Leu Gly Phe Leu Ile Ser Phe Phe Leu
-20 -15 -10

act ggt gta gca gga act cag tca acg cat gag tct ctg aag cct cag 96
Thr Gly Val Ala Gly Thr Gln Ser Thr His Glu Ser Leu Lys Pro Gln
-5 -1 1 5 10

agg gta caa ttt cag tcc cga aat ttt cac aac att ttg caa tgg cag 144
Arg Val Gln Phe Gln Ser Arg Asn Phe His Asn Ile Leu Gln Trp Gln
15 20 25

cct ggg agg gca ctt act ggc aac agc agt gtc tat ttt gtg cag tac 192
Pro Gly Arg Ala Leu Thr Gly Asn Ser Ser Val Tyr Phe Val Gln Tyr
30 35 40

aaa ata tat gga cag aga caa tgg aaa aat aaa gaa gac tgt tgg ggt 240
Lys Ile Tyr Gly Gln Arg Gln Trp Lys Asn Lys Glu Asp Cys Trp Gly

45 50 55

act caa gaa ctc tct tgt gac ctt acc agt gaa acc tca gac ata cag 288
Thr Gln Glu Leu Ser Cys Asp Leu Thr Ser Glu Thr Ser Asp Ile Gln
60 65 70 75

gaa cct tat tac ggg agg agg ggc aaa aat aaa aat aaa ggg aat cct 336
Glu Pro Tyr Tyr Gly Arg Arg Gly Lys Asn Lys Asn Lys Gly Asn Pro
80 85 90

tgg ggg cca aaa caa agt aaa cgg aaa tca aag ggg aac cag aag acc 384
Trp Gly Pro Lys Gln Ser Lys Arg Lys Ser Lys Gly Asn Gln Lys Thr
95 100 105

aac aca gtg act gcc cca gct gcc ctg aag gca ttt gct gga tgt gca 432
Asn Thr Val Thr Ala Pro Ala Ala Leu Lys Ala Phe Ala Gly Cys Ala
110 115 120

aaa ata gat cct cca gtc atg aat ata acc caa gtc aat ggc tct ttg 480
Lys Ile Asp Pro Pro Val Met Asn Ile Thr Gln Val Asn Gly Ser Leu
125 130 135

ttg gta att ctc cat gct cca aat tta cca tat aga tac caa aag gaa 528
Leu Val Ile Leu His Ala Pro Asn Leu Pro Tyr Arg Tyr Gln Lys Glu
140 145 150 155

aaa aat gta tct ata gaa gat tac tat gaa cta cta tac cga gtt ttt 576
Lys Asn Val Ser Ile Glu Asp Tyr Tyr Glu Leu Leu Tyr Arg Val Phe
160 165 170

ata att aac aat tca cta gaa aag gag caa aag gtt tat gaa ggg gct 624
Ile Ile Asn Asn Ser Leu Glu Lys Glu Gln Lys Val Tyr Glu Gly Ala
175 180 185

cac aga gcg gtt gaa att gaa gct cta aca cca cac tcc agc tac tgt 672
His Arg Ala Val Glu Ile Glu Ala Leu Thr Pro His Ser Ser Tyr Cys
190 195 200

gta gtg gct gaa ata tat cag ccc atg tta gac aga aga agt cag aga 720
Val Val Ala Glu Ile Tyr Gln Pro Met Leu Asp Arg Arg Ser Gln Arg
205 210 215

agt gaa gag aga tgt gtg gaa att cca tga 750
Ser Glu Glu Arg Cys Val Glu Ile Pro
220 225

<210> 5
<211> 249
<212> PRT
<213> primate; surmised Homo sapiens

<400> 5
Met Met Pro Lys His Cys Phe Leu Gly Phe Leu Ile Ser Phe Phe Leu
-20 -15 -10

Thr Gly Val Ala Gly Thr Gln Ser Thr His Glu Ser Leu Lys Pro Gln

```
-5                  -1  1               5                   10
Arg Val Gln Phe Gln Ser Arg Asn Phe His Asn Ile Leu Gln Trp Gln
            15                  20                  25

Pro Gly Arg Ala Leu Thr Gly Asn Ser Ser Val Tyr Phe Val Gln Tyr
        30                  35                  40

Lys Ile Tyr Gly Gln Arg Gln Trp Lys Asn Lys Glu Asp Cys Trp Gly
    45                  50                  55

Thr Gln Glu Leu Ser Cys Asp Leu Thr Ser Glu Thr Ser Asp Ile Gln
60                  65                  70                  75

Glu Pro Tyr Tyr Gly Arg Arg Gly Lys Asn Lys Asn Lys Gly Asn Pro
                80                  85                  90

Trp Gly Pro Lys Gln Ser Lys Arg Lys Ser Lys Gly Asn Gln Lys Thr
            95                  100                 105

Asn Thr Val Thr Ala Pro Ala Ala Leu Lys Ala Phe Ala Gly Cys Ala
        110                 115                 120

Lys Ile Asp Pro Pro Val Met Asn Ile Thr Gln Val Asn Gly Ser Leu
    125                 130                 135

Leu Val Ile Leu His Ala Pro Asn Leu Pro Tyr Arg Tyr Gln Lys Glu
140                 145                 150                 155

Lys Asn Val Ser Ile Glu Asp Tyr Tyr Glu Leu Leu Tyr Arg Val Phe
                160                 165                 170

Ile Ile Asn Asn Ser Leu Glu Lys Glu Gln Lys Val Tyr Glu Gly Ala
            175                 180                 185

His Arg Ala Val Glu Ile Glu Ala Leu Thr Pro His Ser Ser Tyr Cys
        190                 195                 200

Val Val Ala Glu Ile Tyr Gln Pro Met Leu Asp Arg Arg Ser Gln Arg
    205                 210                 215

Ser Glu Glu Arg Cys Val Glu Ile Pro
220                 225
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<210> 6
<211> 747
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: reverse translation

<220>
<221> misc_feature
<222> (1)..(747)

<223> n may be a, c, g, or t

<400> 6
atgatgccna arcaytgytt yytnggntty ytnathwsnt tyttyytnac nggngtngcn 60

ggnacncarw snacncayga rwsnytnaar ccncarmgng tncarttyca rwsnmgnaay 120

ttycayaaya thytncartg gcarccnggn mgngcnytna cnggnaayws nwsngtntay 180

ttygtncart ayaarathta yggncarmgn cartggaara ayaargarga ytgytggggn 240

acncargary tnwsntgyga yytnacnwsn garacnwsng ayathcarga rccntaytay 300

ggnmgnmgng gnaaraayaa raayaarggn aayccntggg gnccnaarca rwsnaarmgn 360

aarwsnaarg gnaaycaraa racnaayacn gtnacngcnc cngcngcnyt naargcntty 420

gcnggntgyg cnaarathga yccnccngtn atgaayatha cncargtnaa yggnwsnytn 480

ytngtnathy tncaygcncc naayytnccn taymgntayc araargaraa raaygtnwsn 540

athgargayt aytaygaryt nytntaymgn gtnttyatha thaayaayws nytngaraar 600

garcaraarg tntaygargg ngcncaymgn gcngtngara thgargcnyt nacnccncay 660

wsnwsntayt gygtngtngc ngarathtay carccnatgy tngaymgnmg nwsncarmgn 720

wsngargarm gntgygtnga rathccn 747

<210> 7
<211> 210
<212> PRT
<213> primate

<400> 7
Val Asn Gly Thr Ser Gln Phe Thr Cys Phe Tyr Asn Ser Arg Ala Asn
1 5 10 15

Ile Ser Cys Val Trp Ser Gln Asp Gly Ala Leu Gln Asp Thr Ser Cys
20 25 30

Gln Val His Ala Trp Pro Asp Arg Arg Arg Trp Asn Gln Thr Cys Glu
35 40 45

Leu Leu Pro Val Ser Gln Ala Ser Trp Ala Cys Asn Leu Ile Leu Gly
50 55 60

Ala Pro Asp Ser Gln Lys Leu Thr Thr Val Asp Ile Val Thr Leu Arg
65 70 75 80

Val Leu Cys Arg Glu Gly Val Arg Trp Arg Val Met Ala Ile Gln Asp
85 90 95

Phe Lys Pro Phe Glu Asn Leu Arg Leu Met Ala Pro Ile Ser Leu Gln
100 105 110

Val Val His Val Glu Thr His Arg Cys Asn Ile Ser Trp Glu Ile Ser
115 120 125

Gln Ala Ser His Tyr Phe Glu Arg His Leu Glu Phe Glu Ala Arg Thr
130 135 140

Leu Ser Pro Gly His Thr Trp Glu Glu Ala Pro Leu Leu Thr Leu Lys
145 150 155 160

Gln Lys Gln Glu Trp Ile Cys Leu Glu Thr Leu Thr Pro Asp Thr Gln
165 170 175

Tyr Glu Phe Gln Val Arg Val Lys Pro Leu Gln Gly Glu Phe Thr Thr
180 185 190

Trp Ser Pro Trp Ser Gln Pro Leu Ala Phe Arg Thr Lys Pro Ala Ala
195 200 205

Leu Gly
210

<210> 8
<211> 231
<212> PRT
<213> primate

<400> 8
Ile Cys Ile Cys Thr Cys Val Cys Leu Gly Val Ser Val Thr Gly Glu
1 5 10 15

Gly Gln Gly Pro Arg Ser Arg Thr Phe Thr Cys Leu Thr Asn Asn Ile
20 25 30

Leu Arg Ile Asp Cys His Trp Ser Ala Pro Glu Leu Gly Gln Gly Ser
35 40 45

Ser Pro Trp Leu Leu Phe Thr Ser Asn Gln Ala Pro Gly Gly Thr His
50 55 60

Lys Cys Ile Leu Arg Gly Ser Glu Cys Thr Val Val Leu Pro Pro Glu
65 70 75 80

Ala Val Leu Val Pro Ser Asp Asn Phe Thr Ile Thr Phe His His Cys
85 90 95

Met Ser Gly Arg Glu Gln Val Ser Leu Val Asp Pro Glu Tyr Leu Pro
100 105 110

Arg Arg His Val Lys Leu Asp Pro Pro Ser Asp Leu Gln Ser Asn Ile
115 120 125

Ser Ser Gly His Cys Ile Leu Thr Trp Ser Ile Ser Pro Ala Leu Glu
130 135 140

Pro Met Thr Thr Leu Leu Ser Tyr Glu Leu Ala Phe Lys Lys Gln Glu
145 150 155 160

Glu Ala Trp Glu Gln Ala Gln His Arg Asp His Ile Val Gly Val Thr
165 170 175

Trp Leu Ile Leu Glu Ala Phe Glu Leu Asp Pro Gly Phe Ile His Glu
180 185 190

Ala Arg Leu Arg Val Gln Met Ala Thr Leu Glu Asp Asp Val Val Glu
195 200 205

Glu Glu Arg Tyr Thr Gly Gln Trp Ser Glu Trp Ser Gln Pro Val Cys
210 215 220

Phe Gln Ala Pro Gln Arg Gln
225 230

<210> 9
<211> 216
<212> PRT
<213> primate

<400> 9
Ile Cys Ile Cys Thr Cys Val Cys Leu Gly Val Ser Val Thr Gly Glu
1 5 10 15

Gly Gln Gly Pro Arg Ser Arg Thr Phe Thr Cys Leu Thr Asn Asn Ile
20 25 30

Leu Arg Ile Asp Cys His Trp Ser Ala Pro Glu Leu Gly Gln Gly Thr
35 40 45

Leu His Tyr Trp Tyr Lys Asn Ser Asp Asn Asp Lys Val Gln Lys Cys
50 55 60

Ser His Tyr Leu Phe Ser Glu Glu Ile Thr Ser Gly Cys Gln Leu Gln
65 70 75 80

Lys Lys Glu Ile His Leu Tyr Gln Thr Phe Val Val Gln Leu Gln Asp
85 90 95

Pro Arg Glu Pro Arg Arg Gln Ala Thr Gln Met Leu Lys Leu Gln Asn
100 105 110

Leu Val Ile Pro Trp Ala Pro Glu Asn Leu Thr Leu His Lys Leu Ser
115 120 125

Glu Ser Gln Leu Glu Leu Asn Trp Asn Asn Arg Phe Leu Asn His Cys
130 135 140

Leu Glu His Leu Val Gln Tyr Arg Thr Asp Trp Asp His Ser Trp Thr
145 150 155 160

Glu Gln Ser Val Asp Tyr Arg His Lys Phe Ser Leu Pro Ser Val Asp
165 170 175

Gly Gln Lys Arg Tyr Thr Phe Arg Val Arg Ser Arg Phe Asn Pro Leu

180 185 190

Cys Gly Ser Ala Gln His Trp Ser Glu Trp Ser His Pro Ile His Trp
195 200 205

Gly Ser Asn Thr Ser Lys Glu Asn
210 215

<210> 10
<211> 257
<212> PRT
<213> primate

<400> 10
Leu Leu Ala Ser Asp Ser Glu Pro Leu Lys Cys Phe Ser Arg Thr Phe
1 5 10 15

Glu Asp Leu Thr Cys Phe Trp Asp Glu Glu Glu Ala Ala Pro Ser Gly
20 25 30

Thr Tyr Gln Leu Leu Tyr Ala Tyr Pro Arg Glu Lys Pro Arg Ala Cys
35 40 45

Pro Leu Ser Ser Gln Ser Met Pro His Phe Gly Thr Arg Tyr Val Cys
50 55 60

Gln Phe Pro Asp Gln Glu Glu Val Arg Leu Phe Phe Pro Leu His Leu
65 70 75 80

Trp Val Lys Asn Val Phe Leu Asn Gln Thr Arg Thr Gln Arg Val Leu
85 90 95

Phe Val Asp Ser Val Gly Leu Pro Ala Pro Pro Ser Ile Ile Lys Ala
100 105 110

Met Gly Gly Ser Gln Pro Gly Glu Leu Gln Ile Ser Trp Glu Glu Pro
115 120 125

Ala Pro Glu Ile Ser Asp Phe Leu Arg Tyr Glu Leu Arg Tyr Gly Pro
130 135 140

Arg Asp Pro Lys Asn Ser Thr Gly Pro Thr Val Ile Gln Leu Ile Ala
145 150 155 160

Thr Glu Thr Cys Cys Pro Ala Leu Gln Arg Pro His Ser Ala Ser Ala
165 170 175

Leu Asp Gln Ser Pro Cys Ala Gln Pro Thr Met Pro Trp Gln Asp Gly
180 185 190

Pro Lys Gln Thr Ser Pro Ser Arg Glu Ala Ser Ala Leu Thr Ala Glu
195 200 205

Gly Gly Ser Cys Leu Ile Ser Gly Leu Gln Pro Gly Asn Ser Tyr Trp
210 215 220

Leu Gln Leu Arg Ser Glu Pro Asp Gly Ile Ser Leu Gly Gly Ser Trp
225 230 235 240

Gly Ser Trp Ser Leu Pro Val Thr Val Asp Leu Pro Gly Asp Ala Val
245 250 255

Ala

<210> 11
<211> 217
<212> PRT
<213> primate

<400> 11
Val Ser Gly Glu Ser Gly Tyr Ala Gln Asn Gly Asp Leu Glu Asp Ala
1 5 10 15

Glu Leu Asp Asp Tyr Ser Phe Ser Cys Tyr Ser Gln Leu Glu Val Asn
20 25 30

Gly Ser Gln His Ser Leu Thr Cys Ala Phe Glu Asp Pro Asp Val Asn
35 40 45

Thr Thr Asn Leu Glu Phe Glu Ile Cys Gly Ala Leu Val Glu Val Lys
50 55 60

Cys Leu Asn Phe Arg Lys Leu Gln Glu Ile Tyr Phe Ile Glu Thr Lys
65 70 75 80

Lys Phe Leu Leu Ile Gly Lys Ser Asn Ile Cys Val Lys Val Gly Glu
85 90 95

Lys Ser Leu Thr Cys Lys Lys Ile Asp Leu Thr Thr Ile Val Lys Pro
100 105 110

Glu Ala Pro Phe Asp Leu Ser Val Ile Tyr Arg Glu Gly Ala Asn Asp
115 120 125

Phe Val Val Thr Phe Asn Thr Ser His Leu Gln Lys Lys Tyr Val Lys
130 135 140

Val Leu Met His Asp Val Ala Tyr Arg Gln Glu Lys Asp Glu Asn Lys
145 150 155 160

Trp Thr His Val Asn Leu Ser Ser Thr Lys Leu Thr Leu Leu Gln Arg
165 170 175

Lys Leu Gln Pro Ala Ala Met Tyr Glu Ile Lys Val Arg Ser Ile Pro
180 185 190

Asp His Tyr Phe Lys Gly Phe Trp Ser Glu Trp Ser Pro Ser Tyr Tyr
195 200 205

Phe Arg Thr Pro Glu Ile Asn Asn Ser
210 215

<210> 12
<211> 196
<212> PRT
<213> primate

<400> 12
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Pro Glu Asn Val Arg Met Asn Ser Val Asn Phe Lys Asn Ile Leu Gln
  1               5                  10                  15

Trp Glu Ser Pro Ala Phe Ala Lys Gly Asn Leu Thr Phe Thr Ala Gln
             20                  25                  30

Tyr Leu Ser Tyr Arg Ile Phe Gln Asp Lys Cys Met Asn Thr Thr Leu
         35                  40                  45

Thr Glu Cys Asp Phe Ser Ser Leu Ser Lys Tyr Gly Asp His Thr Leu
     50                  55                  60

Arg Val Arg Ala Glu Phe Ala Asp Glu His Ser Asp Trp Val Asn Ile
 65                  70                  75                  80

Thr Phe Cys Pro Val Asp Asp Thr Ile Ile Gly Pro Pro Gly Met Gln
                 85                  90                  95

Val Glu Val Leu Ala Asp Ser Leu His Met Arg Phe Leu Ala Pro Lys
            100                 105                 110

Ile Glu Asn Glu Tyr Glu Thr Trp Thr Met Lys Asn Val Tyr Asn Ser
        115                 120                 125

Trp Thr Tyr Asn Val Gln Tyr Trp Lys Asn Gly Thr Asp Glu Lys Phe
    130                 135                 140

Gln Ile Thr Pro Gln Tyr Asp Phe Glu Val Leu Arg Asn Leu Glu Pro
145                 150                 155                 160

Trp Thr Thr Tyr Cys Val Gln Val Arg Gly Phe Leu Pro Asp Arg Asn
                165                 170                 175

Lys Ala Gly Glu Trp Ser Glu Pro Val Cys Glu Gln Thr Thr His Asp
            180                 185                 190

Glu Thr Val Pro
        195
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<210> 13
<211> 196
<212> PRT
<213> rodent

<400> 13
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Pro Glu Lys Val Arg Met Asn Ser Val Asn Phe Lys Asn Ile Leu Gln
  1               5                  10                  15
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Trp Glu Val Pro Ala Phe Pro Lys Thr Asn Leu Thr Phe Thr Ala Gln
            20                  25                  30

Tyr Glu Ser Tyr Arg Ser Phe Gln Asp His Cys Lys Arg Thr Ala Ser
        35                  40                  45

Thr Gln Cys Asp Phe Ser His Leu Ser Lys Tyr Gly Asp Tyr Thr Val
    50                  55                  60

Arg Val Arg Ala Glu Leu Ala Asp Glu His Ser Glu Trp Val Asn Val
65                  70                  75                  80

Thr Phe Cys Pro Val Glu Asp Thr Ile Ile Gly Pro Pro Glu Met Gln
                85                  90                  95

Ile Glu Ser Leu Ala Glu Ser Leu His Leu Arg Phe Ser Ala Pro Gln
            100                 105                 110

Ile Glu Asn Glu Pro Glu Thr Trp Thr Leu Lys Asn Ile Tyr Asp Ser
        115                 120                 125

Trp Ala Tyr Arg Val Gln Tyr Trp Lys Asn Gly Thr Asn Glu Lys Phe
    130                 135                 140

Gln Val Val Ser Pro Tyr Asp Ser Glu Val Leu Arg Asn Leu Glu Pro
145                 150                 155                 160

Trp Thr Thr Tyr Cys Ile Gln Val Gln Gly Phe Leu Leu Asp Gln Asn
                165                 170                 175

Arg Thr Gly Glu Trp Ser Glu Pro Ile Cys Glu Arg Thr Gly Asn Asp
            180                 185                 190

Glu Ile Thr Pro
        195


<210> 14
<211> 199
<212> PRT
<213> primate

<400> 14
Pro Gln Lys Val Glu Val Asp Ile Ile Asp Asp Asn Phe Ile Leu Arg
1               5                   10                  15

Trp Asn Arg Ser Asp Glu Ser Val Gly Asn Val Thr Phe Ser Phe Asp
            20                  25                  30

Tyr Gln Lys Thr Gly Met Asp Asn Trp Ile Lys Leu Ser Gly Cys Gln
        35                  40                  45

Asn Ile Thr Ser Thr Lys Cys Asn Phe Ser Ser Leu Lys Leu Asn Val
    50                  55                  60

Tyr Glu Glu Ile Lys Leu Arg Ile Arg Ala Glu Lys Glu Asn Thr Ser
65                  70                  75                  80
```

Ser Trp Tyr Glu Val Asp Ser Phe Thr Pro Phe Arg Lys Ala Gln Ile
85 90 95

Gly Pro Pro Glu Val His Leu Glu Ala Glu Asp Lys Ala Ile Val Ile
100 105 110

His Ile Ser Pro Gly Thr Lys Asp Ser Val Met Trp Ala Leu Asp Gly
115 120 125

Leu Ser Phe Thr Tyr Ser Leu Leu Ile Trp Lys Asn Ser Ser Gly Val
130 135 140

Glu Glu Arg Ile Glu Asn Ile Tyr Ser Arg His Lys Ile Tyr Lys Leu
145 150 155 160

Ser Pro Glu Thr Thr Tyr Cys Leu Lys Val Lys Ala Ala Leu Leu Thr
165 170 175

Ser Trp Lys Ile Gly Val Tyr Ser Pro Val His Cys Ile Lys Thr Thr
180 185 190

Val Glu Asn Glu Leu Pro Pro
195

<210> 15
<211> 200
<212> PRT
<213> rodent

<400> 15
Pro Glu Asn Ile Asp Val Tyr Ile Ile Asp Asp Asn Tyr Thr Leu Lys
1 5 10 15

Trp Ser Ser His Gly Glu Ser Met Gly Ser Val Thr Phe Ser Ala Glu
20 25 30

Tyr Arg Thr Lys Asp Glu Ala Lys Trp Leu Lys Val Pro Glu Cys Gln
35 40 45

His Thr Thr Thr Thr Lys Cys Glu Phe Ser Leu Leu Asp Thr Asn Val
50 55 60

Tyr Ile Lys Thr Gln Phe Arg Val Arg Ala Glu Glu Gly Asn Ser Thr
65 70 75 80

Ser Ser Trp Asn Glu Val Asp Pro Phe Ile Pro Phe Tyr Thr Ala His
85 90 95

Met Ser Pro Pro Glu Val Arg Leu Glu Ala Glu Asp Lys Ala Ile Leu
100 105 110

Val His Ile Ser Pro Pro Gly Gln Asp Gly Asn Met Trp Ala Leu Glu
115 120 125

Lys Pro Ser Phe Ser Tyr Thr Ile Arg Ile Trp Gln Lys Ser Ser Ser

130 135 140

Asp Lys Lys Thr Ile Asn Ser Thr Tyr Tyr Val Glu Lys Ile Pro Glu
145 150 155 160

Leu Leu Pro Glu Thr Thr Tyr Cys Leu Glu Val Lys Ala Ile His Pro
165 170 175

Ser Leu Lys Lys His Ser Asn Tyr Ser Thr Val Gln Cys Ile Ser Thr
180 185 190

Thr Val Ala Asn Lys Met Pro Val
195 200

<210> 16
<211> 214
<212> PRT
<213> primate

<400> 16
Pro Thr Asn Val Thr Ile Glu Ser Tyr Asn Met Asn Pro Ile Val Tyr
1 5 10 15

Trp Glu Tyr Gln Ile Met Pro Gln Val Pro Val Phe Thr Val Glu Val
20 25 30

Lys Asn Tyr Gly Val Lys Asn Ser Glu Trp Ile Asp Ala Cys Ile Asn
35 40 45

Ile Ser His His Tyr Cys Asn Ile Ser Asp His Val Gly Asp Pro Ser
50 55 60

Asn Ser Leu Trp Val Arg Val Lys Ala Arg Val Gly Gln Lys Glu Ser
65 70 75 80

Ala Tyr Ala Lys Ser Glu Glu Phe Ala Val Cys Arg Asp Gly Lys Ile
85 90 95

Gly Pro Pro Lys Leu Asp Ile Arg Lys Glu Glu Lys Gln Ile Met Ile
100 105 110

Asp Ile Phe His Pro Ser Val Phe Val Asn Gly Asp Glu Gln Glu Val
115 120 125

Asp Tyr Asp Pro Glu Thr Thr Cys Tyr Ile Arg Val Tyr Asn Val Tyr
130 135 140

Val Arg Met Asn Gly Ser Glu Ile Gln Tyr Lys Ile Leu Thr Gln Lys
145 150 155 160

Glu Asp Asp Cys Asp Glu Ile Gln Cys Gln Leu Ala Ile Pro Val Ser
165 170 175

Ser Leu Asn Ser Gln Tyr Cys Val Ser Ala Glu Gly Val Leu His Val
180 185 190

Trp Gly Val Thr Thr Glu Lys Ser Lys Glu Val Cys Ile Thr Ile Phe
195 200 205

Asn Ser Ser Ile Lys Gly
210

<210> 17
<211> 213
<212> PRT
<213> rodent

<400> 17
Pro Thr Asn Val Leu Ile Lys Ser Tyr Asn Leu Asn Pro Val Val Cys
1 5 10 15

Trp Glu Tyr Gln Asn Met Ser Gln Thr Pro Ile Phe Thr Val Gln Val
20 25 30

Lys Val Tyr Ser Gly Ser Trp Thr Asp Ser Cys Thr Asn Ile Ser Asp
35 40 45

His Cys Cys Asn Ile Tyr Gly Gln Ile Met Tyr Pro Asp Val Ser Ala
50 55 60

Trp Ala Arg Val Lys Ala Lys Val Gly Gln Lys Glu Ser Asp Tyr Ala
65 70 75 80

Arg Ser Lys Glu Phe Leu Met Cys Leu Lys Gly Lys Val Gly Pro Pro
85 90 95

Gly Leu Glu Ile Arg Arg Lys Lys Glu Glu Gln Leu Ser Val Leu Val
100 105 110

Phe His Pro Glu Val Val Val Asn Gly Glu Ser Gln Gly Thr Met Phe
115 120 125

Gly Asp Gly Ser Thr Cys Tyr Thr Phe Asp Tyr Thr Val Tyr Val Glu
130 135 140

His Asn Arg Ser Gly Glu Ile Leu His Thr Lys His Thr Val Glu Lys
145 150 155 160

Glu Glu Cys Asn Glu Thr Leu Cys Glu Leu Asn Ile Ser Val Ser Thr
165 170 175

Leu Asp Ser Arg Tyr Cys Ile Ser Val Asp Gly Ile Ser Ser Phe Trp
180 185 190

Gln Val Arg Thr Glu Lys Ser Lys Asp Val Cys Ile Pro Pro Phe His
195 200 205

Asp Asp Arg Lys Asp
210

<210> 18

<211> 207
<212> PRT
<213> rodent

<400> 18
Pro Ser Tyr Val Trp Phe Glu Ala Arg Phe Phe Gln His Ile Leu His
1 5 10 15

Trp Lys Pro Ile Pro Asn Gln Ser Glu Ser Thr Tyr Tyr Glu Val Ala
20 25 30

Leu Lys Gln Tyr Gly Asn Ser Thr Trp Asn Asp Ile His Ile Cys Arg
35 40 45

Lys Ala Gln Ala Leu Ser Cys Asp Leu Thr Thr Phe Thr Leu Asp Leu
50 55 60

Tyr His Arg Ser Tyr Gly Tyr Arg Ala Arg Val Arg Ala Val Asp Asn
65 70 75 80

Ser Gln Tyr Ser Asn Trp Thr Thr Thr Glu Thr Arg Phe Thr Val Asp
85 90 95

Glu Val Ile Leu Thr Val Asp Ser Val Thr Leu Lys Ala Met Asp Gly
100 105 110

Ile Ile Tyr Gly Thr Ile His Pro Pro Arg Pro Thr Ile Thr Pro Ala
115 120 125

Gly Asp Glu Tyr Glu Gln Val Phe Lys Asp Leu Arg Val Tyr Lys Ile
130 135 140

Ser Ile Arg Lys Phe Ser Glu Leu Lys Asn Ala Thr Lys Arg Val Lys
145 150 155 160

Gln Glu Thr Phe Thr Leu Thr Val Pro Ile Gly Val Arg Lys Phe Cys
165 170 175

Val Lys Val Leu Pro Arg Leu Glu Ser Arg Ile Asn Lys Ala Glu Trp
180 185 190

Ser Glu Glu Gln Cys Leu Leu Ile Thr Thr Glu Gln Tyr Phe Thr
195 200 205

<210> 19
<211> 204
<212> PRT
<213> primate

<400> 19
Pro Pro Ser Val Trp Phe Glu Ala Glu Phe Phe His His Ile Leu His
1 5 10 15

Trp Thr Pro Ile Pro Asn Gln Ser Glu Ser Thr Cys Tyr Glu Val Ala
20 25 30

Leu Leu Arg Tyr Gly Ile Glu Ser Trp Asn Ser Ile Ser Asn Cys Ser
35 40 45

Gln Thr Leu Ser Tyr Asp Leu Thr Ala Val Thr Leu Asp Leu Tyr His
50 55 60

Ser Asn Gly Tyr Arg Ala Arg Val Arg Ala Val Asp Gly Ser Arg His
65 70 75 80

Ser Asn Trp Thr Val Thr Asn Thr Arg Phe Ser Val Asp Glu Val Thr
85 90 95

Leu Thr Val Gly Ser Val Asn Leu Glu Ile His Asn Gly Phe Ile Leu
100 105 110

Gly Lys Ile Gln Leu Pro Arg Pro Lys Met Ala Pro Ala Asn Asp Thr
115 120 125

Tyr Glu Ser Ile Phe Ser His Phe Arg Glu Tyr Glu Ile Ala Ile Arg
130 135 140

Lys Val Pro Gly Asn Phe Thr Phe Thr His Lys Lys Val Lys His Glu
145 150 155 160

Asn Phe Ser Leu Leu Thr Ser Gly Glu Val Gly Glu Phe Cys Val Gln
165 170 175

Val Lys Pro Ser Val Ala Ser Arg Ser Asn Lys Gly Met Trp Ser Lys
180 185 190

Glu Glu Cys Ile Ser Leu Thr Arg Gln Tyr Phe Thr
195 200

<210> 20
<211> 208
<212> PRT
<213> primate

<400> 20
Pro Leu Asn Pro Arg Leu His Leu Tyr Asn Asp Glu Gln Ile Leu Thr
1 5 10 15

Trp Glu Pro Ser Pro Ser Ser Asn Asp Pro Arg Pro Val Val Tyr Gln
20 25 30

Val Glu Tyr Ser Phe Ile Asp Gly Ser Trp His Arg Leu Leu Glu Pro
35 40 45

Asn Cys Thr Asp Ile Thr Glu Thr Lys Cys Asp Leu Thr Gly Gly Gly
50 55 60

Arg Leu Lys Leu Phe Pro His Pro Phe Thr Val Phe Leu Arg Val Arg
65 70 75 80

Ala Lys Arg Gly Asn Leu Thr Ser Lys Trp Val Gly Leu Glu Pro Phe
85 90 95

Gln His Tyr Glu Asn Val Thr Val Gly Pro Pro Lys Asn Ile Ser Val
100 105 110

Thr Pro Gly Lys Gly Ser Leu Val Ile His Phe Ser Pro Pro Phe Asp
115 120 125

Val Phe His Gly Ala Thr Phe Gln Tyr Leu Val His Tyr Trp Glu Lys
130 135 140

Ser Glu Thr Gln Gln Glu Gln Val Glu Gly Pro Phe Lys Ser Asn Ser
145 150 155 160

Ile Val Leu Gly Asn Leu Lys Pro Tyr Arg Val Tyr Cys Leu Gln Thr
165 170 175

Glu Ala Gln Leu Ile Leu Lys Asn Lys Lys Ile Arg Pro His Gly Leu
180 185 190

Leu Ser Asn Val Ser Cys His Glu Thr Thr Ala Asn Ala Ser Ala Arg
195 200 205

<210> 21
<211> 207
<212> PRT
<213> primate

<400> 21
Pro Ala Asn Ile Thr Phe Leu Ser Ile Asn Met Lys Asn Val Leu Gln
1 5 10 15

Trp Thr Pro Pro Glu Gly Leu Gln Gly Val Lys Val Thr Tyr Thr Val
20 25 30

Gln Tyr Phe Ile Tyr Gly Gln Lys Lys Trp Leu Asn Lys Ser Glu Cys
35 40 45

Arg Asn Ile Asn Arg Thr Tyr Cys Asp Leu Ser Ala Glu Thr Ser Asp
50 55 60

Tyr Glu His Gln Tyr Tyr Ala Lys Val Lys Ala Ile Trp Gly Thr Lys
65 70 75 80

Cys Ser Lys Trp Ala Glu Ser Gly Arg Phe Tyr Pro Phe Leu Glu Thr
85 90 95

Gln Ile Gly Pro Pro Glu Val Ala Leu Thr Thr Asp Glu Lys Ser Ile
100 105 110

Ser Val Val Leu Thr Ala Pro Glu Lys Trp Lys Arg Asn Pro Glu Asp
115 120 125

Leu Pro Val Ser Met Gln Gln Ile Tyr Ser Asn Leu Lys Tyr Asn Val

130 135 140

Ser Val Leu Asn Thr Lys Ser Asn Arg Thr Trp Ser Gln Cys Val Thr
145 150 155 160

Asn His Thr Leu Val Leu Thr Trp Leu Glu Pro Asn Thr Leu Tyr Cys
165 170 175

Val His Val Glu Ser Phe Val Pro Gly Pro Pro Arg Arg Ala Gln Pro
180 185 190

Ser Glu Lys Gln Cys Ala Arg Thr Leu Lys Asp Gln Ser Ser Glu
195 200 205

<210> 22
<211> 234
<212> PRT
<213> primate

<400> 22
Leu Gln His Val Lys Phe Gln Ser Ser Asn Phe Glu Asn Ile Leu Thr
1 5 10 15

Trp Asp Ser Gly Pro Glu Gly Thr Pro Asp Thr Val Tyr Ser Ile Glu
20 25 30

Tyr Lys Thr Tyr Gly Glu Arg Asp Trp Val Ala Lys Lys Gly Cys Gln
35 40 45

Arg Ile Thr Arg Lys Ser Cys Asn Leu Thr Val Glu Thr Gly Asn Leu
50 55 60

Thr Glu Leu Tyr Tyr Ala Arg Val Thr Ala Val Ser Ala Gly Gly Arg
65 70 75 80

Ser Ala Thr Lys Met Thr Asp Arg Phe Ser Ser Leu Gln His Thr Thr
85 90 95

Leu Lys Pro Pro Asp Val Thr Cys Ile Ser Lys Val Arg Ser Ile Gln
100 105 110

Met Ile Val His Pro Thr Pro Thr Pro Ile Arg Ala Gly Asp Gly His
115 120 125

Arg Leu Thr Leu Glu Asp Ile Phe His Asp Leu Phe Tyr His Leu Glu
130 135 140

Leu Gln Val Asn Arg Thr Tyr Gln Met His Leu Gly Gly Lys Gln Arg
145 150 155 160

Glu Tyr Glu Phe Phe Gly Leu Thr Pro Asp Thr Glu Phe Leu Gly Thr
165 170 175

Ile Met Ile Cys Val Pro Thr Trp Ala Lys Glu Ser Ala Pro Tyr Met
180 185 190

Cys Arg Val Lys Thr Leu Pro Asp Arg Thr Trp Thr Tyr Ser Phe Ser
195 200 205

Gly Ala Phe Leu Phe Ser Met Gly Phe Leu Val Ala Val Leu Cys Tyr
210 215 220

Leu Ser Tyr Arg Tyr Val Thr Lys Pro Pro
225 230

<210> 23
<211> 201
<212> PRT
<213> primate

<400> 23
Ser Cys Thr Phe Lys Ile Ser Leu Arg Asn Phe Arg Ser Ile Leu Ser
1 5 10 15

Trp Glu Leu Lys Asn His Ser Ile Val Pro Thr His Tyr Thr Leu Leu
20 25 30

Tyr Thr Ile Met Ser Lys Pro Glu Asp Leu Lys Val Val Lys Asn Cys
35 40 45

Ala Asn Thr Thr Arg Ser Phe Cys Asp Leu Thr Asp Glu Trp Arg Ser
50 55 60

Thr His Glu Ala Tyr Val Thr Val Leu Glu Gly Phe Ser Gly Asn Thr
65 70 75 80

Thr Leu Phe Ser Cys Ser His Asn Phe Trp Leu Ala Ile Asp Met Ser
85 90 95

Phe Glu Pro Pro Glu Phe Glu Ile Val Gly Phe Thr Asn His Ile Asn
100 105 110

Val Met Val Lys Phe Pro Ser Ile Val Glu Glu Glu Leu Gln Phe Asp
115 120 125

Leu Ser Leu Val Ile Glu Glu Gln Ser Glu Gly Ile Val Lys Lys His
130 135 140

Lys Pro Glu Ile Lys Gly Asn Met Ser Gly Asn Phe Thr Tyr Ile Ile
145 150 155 160

Asp Lys Leu Ile Pro Asn Thr Asn Tyr Cys Val Ser Val Tyr Leu Glu
165 170 175

His Ser Asp Glu Gln Ala Val Ile Lys Ser Pro Leu Lys Cys Thr Leu
180 185 190

Leu Pro Pro Gly Gln Glu Ser Glu Ser
195 200

<210> 24

<211> 1617
<212> DNA
<213> primate; surmised Homo sapiens

<220>
<221> CDS
<222> (1)..(1614)

<220>
<221> mat_peptide
<222> (61)..(1614)

<220>
<221> misc_feature
<222> (1)..(1617)
<223> n may be a, c, g, or t; translated amino acid
depends on genetic code

<400> 24
atg ccg cgt ggc tgg gcc gcc ccc ttg ctc ctg ctg ctg ctc cag gga 48
Met Pro Arg Gly Trp Ala Ala Pro Leu Leu Leu Leu Leu Leu Gln Gly
-20 -15 -10 -5

ggc tgg ggc tgc ccc gac ctc gtc tgc tac acc gat tac ctc cag acg 96
Gly Trp Gly Cys Pro Asp Leu Val Cys Tyr Thr Asp Tyr Leu Gln Thr
-1 1 5 10

gtc atc tgc atc ctg gaa atg tgg aac ctc cac ccc agc acg ctc acc 144
Val Ile Cys Ile Leu Glu Met Trp Asn Leu His Pro Ser Thr Leu Thr
15 20 25

ctt acc tgg caa gac cag tat gaa gag ctg aag gac gag gcc acc tcc 192
Leu Thr Trp Gln Asp Gln Tyr Glu Glu Leu Lys Asp Glu Ala Thr Ser
30 35 40

tgc agc ctc cac agg tcg gcc cac aat gcc acg cat gcc acc tac acc 240
Cys Ser Leu His Arg Ser Ala His Asn Ala Thr His Ala Thr Tyr Thr
45 50 55 60

tgc cac atg gat gta ttc cac ttc atg gcc gac gac att ttc agt gtc 288
Cys His Met Asp Val Phe His Phe Met Ala Asp Asp Ile Phe Ser Val
65 70 75

aac atc aca gac cag tct ggc aac tac tcc cag gan tgt ggc agc ttt 336
Asn Ile Thr Asp Gln Ser Gly Asn Tyr Ser Gln Xaa Cys Gly Ser Phe
80 85 90

ctc ctg gct gag agc atc aag ccg gct ccc cct ttc aac gtg act gtg 384
Leu Leu Ala Glu Ser Ile Lys Pro Ala Pro Pro Phe Asn Val Thr Val
95 100 105

acc ttc tca gga cag tat aat atn tcc tgg cgc tca gat tac gaa gac 432
Thr Phe Ser Gly Gln Tyr Asn Xaa Ser Trp Arg Ser Asp Tyr Glu Asp
110 115 120

cct gcc ttc tac atg ctg aaa ggc aag ctt caa tat gag ctg cag tac 480
Pro Ala Phe Tyr Met Leu Lys Gly Lys Leu Gln Tyr Glu Leu Gln Tyr

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125                 130                 135                 140

agg aac cgg gga gac ccc tgg gct gtg agt ccg agg aga aag ctg atc    528
Arg Asn Arg Gly Asp Pro Trp Ala Val Ser Pro Arg Arg Lys Leu Ile
                145                 150                 155

tca gtg gac tca aga agt gtc tcc ctc ctc ccc ctg gag ttc cgc aaa    576
Ser Val Asp Ser Arg Ser Val Ser Leu Leu Pro Leu Glu Phe Arg Lys
            160                 165                 170

gac tcg agc tat gag ctg can gtg cgg gca ggg ccc atg cct ggc tcc    624
Asp Ser Ser Tyr Glu Leu Xaa Val Arg Ala Gly Pro Met Pro Gly Ser
        175                 180                 185

tcc tac cag ggg acc tgg agt gaa tgg agt gac ccg gtc atc tgt cag    672
Ser Tyr Gln Gly Thr Trp Ser Glu Trp Ser Asp Pro Val Ile Cys Gln
    190                 195                 200

acc cag tca gag gag tta aag gaa ggc tgg aac cct cac ctg ctg ctt    720
Thr Gln Ser Glu Glu Leu Lys Glu Gly Trp Asn Pro His Leu Leu Leu
205                 210                 215                 220

ctc ctc ctg ctt gtc ata gtc ttc att cct gcc ttc tgg agc ctg aag    768
Leu Leu Leu Leu Val Ile Val Phe Ile Pro Ala Phe Trp Ser Leu Lys
                225                 230                 235

acc cat cca ttg tgg agg cta tgg aag aag ata tgg gcc gtc ccc agc    816
Thr His Pro Leu Trp Arg Leu Trp Lys Lys Ile Trp Ala Val Pro Ser
            240                 245                 250

cct gag cgg ttc ttc atg ccc ctg tac aag ggc tgc agc gga gac ttc    864
Pro Glu Arg Phe Phe Met Pro Leu Tyr Lys Gly Cys Ser Gly Asp Phe
        255                 260                 265

aag aaa tgg gtg ggt gca ccc ttc act ggc tcc agc ctg gag ctg gga    912
Lys Lys Trp Val Gly Ala Pro Phe Thr Gly Ser Ser Leu Glu Leu Gly
    270                 275                 280

ccc tgg agc cca gag gtg ccc tcc acc ctg gag gtg tac agc tgc cac    960
Pro Trp Ser Pro Glu Val Pro Ser Thr Leu Glu Val Tyr Ser Cys His
285                 290                 295                 300

cca cca cgg agc ccg gcc aag agg ctg cag ctc acg gag cta caa gaa    1008
Pro Pro Arg Ser Pro Ala Lys Arg Leu Gln Leu Thr Glu Leu Gln Glu
                305                 310                 315

cca gca gag ctg gtg gag tct gac ggt gtg ccc aag ccc agc ttc tgg    1056
Pro Ala Glu Leu Val Glu Ser Asp Gly Val Pro Lys Pro Ser Phe Trp
            320                 325                 330

ccg aca gcc cag aac tcg ggg ggc tca gct tac agt gag gag agg gat    1104
Pro Thr Ala Gln Asn Ser Gly Gly Ser Ala Tyr Ser Glu Glu Arg Asp
        335                 340                 345

cgg cca tac ggc ctg gtg tcc att gac aca gtg act gtg cta gat gca    1152
Arg Pro Tyr Gly Leu Val Ser Ile Asp Thr Val Thr Val Leu Asp Ala
    350                 355                 360
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gag ggg cca tgc acc tgg ccc tgc agc tgt gag gat gac ggc tac cca 1200
Glu Gly Pro Cys Thr Trp Pro Cys Ser Cys Glu Asp Asp Gly Tyr Pro
365 370 375 380

gcc ctg gac ctg gat gct ggc ctg gag ccc agc cca ggc cta gag gac 1248
Ala Leu Asp Leu Asp Ala Gly Leu Glu Pro Ser Pro Gly Leu Glu Asp
385 390 395

cca ctc ttg gat gca ggg acc aca gtc ctg tcc tgt ggc tgt gtc tca 1296
Pro Leu Leu Asp Ala Gly Thr Thr Val Leu Ser Cys Gly Cys Val Ser
400 405 410

gct ggc agc cct ggg cta gga ggg ccc ctg gga agc ctc ctg gac aga 1344
Ala Gly Ser Pro Gly Leu Gly Gly Pro Leu Gly Ser Leu Leu Asp Arg
415 420 425

cta aag cca ccc ctt gca gat ggg gag gac tgg gct ggg gga ctg ccc 1392
Leu Lys Pro Pro Leu Ala Asp Gly Glu Asp Trp Ala Gly Gly Leu Pro
430 435 440

tgg ggt ggc cgg tca cct gga ggg gtc tca gag agt gag gcg ggc tca 1440
Trp Gly Gly Arg Ser Pro Gly Gly Val Ser Glu Ser Glu Ala Gly Ser
445 450 455 460

ccc ctg gcc ggc ctg gat atg gac acg ttt gac agt ggc ttt gtg ggc 1488
Pro Leu Ala Gly Leu Asp Met Asp Thr Phe Asp Ser Gly Phe Val Gly
465 470 475

tct gac tgc agc agc cct gtg gag tgt gac ttc acc agc ccc ggg gac 1536
Ser Asp Cys Ser Ser Pro Val Glu Cys Asp Phe Thr Ser Pro Gly Asp
480 485 490

gaa gga ccc ccc cgg agc tac ctc cgc cag tgg gtg gtc att cct ccg 1584
Glu Gly Pro Pro Arg Ser Tyr Leu Arg Gln Trp Val Val Ile Pro Pro
495 500 505

cca ctt tcg agc cct gga ccc cag gcc agc taa 1617
Pro Leu Ser Ser Pro Gly Pro Gln Ala Ser
510 515

<210> 25
<211> 538
<212> PRT
<213> primate; surmised Homo sapiens

<400> 25
Met Pro Arg Gly Trp Ala Ala Pro Leu Leu Leu Leu Leu Leu Gln Gly
-20 -15 -10 -5

Gly Trp Gly Cys Pro Asp Leu Val Cys Tyr Thr Asp Tyr Leu Gln Thr
-1 1 5 10

Val Ile Cys Ile Leu Glu Met Trp Asn Leu His Pro Ser Thr Leu Thr
15 20 25

Leu Thr Trp Gln Asp Gln Tyr Glu Glu Leu Lys Asp Glu Ala Thr Ser
30 35 40

Cys Ser Leu His Arg Ser Ala His Asn Ala Thr His Ala Thr Tyr Thr
45 50 55 60

Cys His Met Asp Val Phe His Phe Met Ala Asp Asp Ile Phe Ser Val
65 70 75

Asn Ile Thr Asp Gln Ser Gly Asn Tyr Ser Gln Xaa Cys Gly Ser Phe
80 85 90

Leu Leu Ala Glu Ser Ile Lys Pro Ala Pro Pro Phe Asn Val Thr Val
95 100 105

Thr Phe Ser Gly Gln Tyr Asn Xaa Ser Trp Arg Ser Asp Tyr Glu Asp
110 115 120

Pro Ala Phe Tyr Met Leu Lys Gly Lys Leu Gln Tyr Glu Leu Gln Tyr
125 130 135 140

Arg Asn Arg Gly Asp Pro Trp Ala Val Ser Pro Arg Arg Lys Leu Ile
145 150 155

Ser Val Asp Ser Arg Ser Val Ser Leu Leu Pro Leu Glu Phe Arg Lys
160 165 170

Asp Ser Ser Tyr Glu Leu Xaa Val Arg Ala Gly Pro Met Pro Gly Ser
175 180 185

Ser Tyr Gln Gly Thr Trp Ser Glu Trp Ser Asp Pro Val Ile Cys Gln
190 195 200

Thr Gln Ser Glu Glu Leu Lys Glu Gly Trp Asn Pro His Leu Leu Leu
205 210 215 220

Leu Leu Leu Leu Val Ile Val Phe Ile Pro Ala Phe Trp Ser Leu Lys
225 230 235

Thr His Pro Leu Trp Arg Leu Trp Lys Lys Ile Trp Ala Val Pro Ser
240 245 250

Pro Glu Arg Phe Phe Met Pro Leu Tyr Lys Gly Cys Ser Gly Asp Phe
255 260 265

Lys Lys Trp Val Gly Ala Pro Phe Thr Gly Ser Ser Leu Glu Leu Gly
270 275 280

Pro Trp Ser Pro Glu Val Pro Ser Thr Leu Glu Val Tyr Ser Cys His
285 290 295 300

Pro Pro Arg Ser Pro Ala Lys Arg Leu Gln Leu Thr Glu Leu Gln Glu
305 310 315

Pro Ala Glu Leu Val Glu Ser Asp Gly Val Pro Lys Pro Ser Phe Trp
320 325 330

Pro Thr Ala Gln Asn Ser Gly Gly Ser Ala Tyr Ser Glu Glu Arg Asp
335 340 345

Arg Pro Tyr Gly Leu Val Ser Ile Asp Thr Val Thr Val Leu Asp Ala
350 355 360

Glu Gly Pro Cys Thr Trp Pro Cys Ser Cys Glu Asp Asp Gly Tyr Pro
365 370 375 380

Ala Leu Asp Leu Asp Ala Gly Leu Glu Pro Ser Pro Gly Leu Glu Asp
385 390 395

Pro Leu Leu Asp Ala Gly Thr Thr Val Leu Ser Cys Gly Cys Val Ser
400 405 410

Ala Gly Ser Pro Gly Leu Gly Gly Pro Leu Gly Ser Leu Leu Asp Arg
415 420 425

Leu Lys Pro Pro Leu Ala Asp Gly Glu Asp Trp Ala Gly Gly Leu Pro
430 435 440

Trp Gly Gly Arg Ser Pro Gly Gly Val Ser Glu Ser Glu Ala Gly Ser
445 450 455 460

Pro Leu Ala Gly Leu Asp Met Asp Thr Phe Asp Ser Gly Phe Val Gly
465 470 475

Ser Asp Cys Ser Ser Pro Val Glu Cys Asp Phe Thr Ser Pro Gly Asp
480 485 490

Glu Gly Pro Pro Arg Ser Tyr Leu Arg Gln Trp Val Val Ile Pro Pro
495 500 505

Pro Leu Ser Ser Pro Gly Pro Gln Ala Ser
510 515

<210> 26
<211> 1614
<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature
<222> (1)..(1614)
<223> n may be a, c, g, or t

<220>
<223> Description of Artificial Sequence:reverse
translation

<400> 26
atgccnmgng gntgggcngc nccnytnytn ytnytnytny tncarggngg ntggggntgy 60

ccngayytng tntgytayac ngaytayytn caracngtna thtgyathyt ngaratgtgg 120

aayytncayc cnwsnacnyt nacnytnacn tggcargayc artaygarga rytnaargay 180

gargcnacnw sntgywsnyt ncaymgnwsn gcncayaayg cnacncaygc nacntayacn 240
tgycayatgg aygtnttyca yttyatggcn gaygayatht tywsngtnaa yathacngay 300
carwsnggna aytaywsnca rnnntgyggn wsnttyytny tngcngarws nathaarccn 360
gcnccnccnt tyaaygtnac ngtnacntty wsnggncart ayaaynnnws ntggmgnwsn 420
gaytaygarg ayccngcntt ytayatgytn aarggnaary tncartayga rytncartay 480
mgnaaymgng gngayccntg ggcngtnwsn ccnmgnmgna arytnathws ngtngaywsn 540
mgnwsngtnw snytnytncc nytngartty mgnaargayw snwsntayga rytnnnngtn 600
mgngcnggnc cnatgccngg nwsnwsntay carggnacnt ggwsngartg gwsngayccn 660
gtnathtgyc aracncarws ngargarytn aargarggnt ggaayccnca yytnytnytn 720
ytnytnytny tngtnathgt nttyathccn gcnttytggw snytnaarac ncayccnytn 780
tggmgnytnt ggaaraarat htgggcngtn ccnwsnccng armgnttytt yatgccnytn 840
tayaarggnt gywsnggnga yttyaaraar tgggtnggng cnccnttyac nggnwsnwsn 900
ytngarytng gnccntggws nccngargtn ccnwsnacny tngargtnta ywsntgycay 960
ccnccnmgnw snccngcnaa rmgnytncar ytnacngary tncargarcc ngcngarytn 1020
gtngarwsng ayggngtncc naarccnwsn ttytggccna cngcncaraa ywsnggnggn 1080
wsngcntayw sngargarmg ngaymgnccn tayggnytng tnwsnathga yacngtnacn 1140
gtnytngayg cngarggncc ntgyacntgg ccntgywsnt gygargayga yggntayccn 1200
gcnytngayy tngaygcngg nytngarccn wsnccnggny tngargaycc nytnytngay 1260
gcnggnacna cngtnytnws ntgyggntgy gtnwsngcng gnwsnccngg nytnggnggn 1320
ccnytnggnw snytnytnga ymgnytnaar ccnccnytng cngayggnga rgaytgggcn 1380
ggnggnytnc cntggggngg nmgnwsnccn ggnggngtnw sngarwsnga rgcnggnwsn 1440
ccnytngcng gnytngayat ggayacntty gaywsnggnt tygtnggnws ngaytgywsn 1500
wsnccngtng artgygaytt yacnwsnccn ggngaygarg gnccnccnmg nwsntayytn 1560
mgncartggg tngtnathcc nccnccnytn wsnwsnccng gnccncargc nwsn 1614

<210> 27
<211> 696
<212> DNA
<213> primate; surmised Homo sapiens

<220>
<221> CDS

<222> (1)..(693)

<220>
<221> mat_peptide
<222> (64)..(693)

<400> 27
atg atg cct aaa cat tgc ttt cta ggc ttc ctc atc agt ttc ttc ctt 48
Met Met Pro Lys His Cys Phe Leu Gly Phe Leu Ile Ser Phe Phe Leu
-20 -15 -10

act ggt gta gca gga act cag tca acg cat gag tct ctg aag cct cag 96
Thr Gly Val Ala Gly Thr Gln Ser Thr His Glu Ser Leu Lys Pro Gln
-5 -1 1 5 10

agg gta caa ttt cag tcc cga aat ttt cac aac att ttg caa tgg cag 144
Arg Val Gln Phe Gln Ser Arg Asn Phe His Asn Ile Leu Gln Trp Gln
15 20 25

ccc ggg agg gca ctt act ggc aac agc agt gtc tat ttt gtg cag tac 192
Pro Gly Arg Ala Leu Thr Gly Asn Ser Ser Val Tyr Phe Val Gln Tyr
30 35 40

aaa ata tat gga cag aga caa tgg aaa aat aaa gaa gac tgt tgg ggt 240
Lys Ile Tyr Gly Gln Arg Gln Trp Lys Asn Lys Glu Asp Cys Trp Gly
45 50 55

act caa gaa ctc tct tgt gac ctt acc agt gaa acc tca gac ata cag 288
Thr Gln Glu Leu Ser Cys Asp Leu Thr Ser Glu Thr Ser Asp Ile Gln
60 65 70 75

gaa cct tat tac ggg agg gtg agg gcg gcc tcg gct ggg agc tac tca 336
Glu Pro Tyr Tyr Gly Arg Val Arg Ala Ala Ser Ala Gly Ser Tyr Ser
80 85 90

gaa tgg agc atg acg ccg cgg ttc act ccc tgg tgg gaa aca aaa ata 384
Glu Trp Ser Met Thr Pro Arg Phe Thr Pro Trp Trp Glu Thr Lys Ile
95 100 105

gat cct cca gtc atg aat ata acc caa gtc aat ggc tct ttg ttg gta 432
Asp Pro Pro Val Met Asn Ile Thr Gln Val Asn Gly Ser Leu Leu Val
110 115 120

att ctc cat gct cca aat tta cca tat aga tac caa aag gaa aaa aat 480
Ile Leu His Ala Pro Asn Leu Pro Tyr Arg Tyr Gln Lys Glu Lys Asn
125 130 135

gta tct ata gaa gat tac tat gaa cta cta tac cga gtt ttt ata att 528
Val Ser Ile Glu Asp Tyr Tyr Glu Leu Leu Tyr Arg Val Phe Ile Ile
140 145 150 155

aac aat tca cta gaa aag gag caa aag gtt tat gaa ggg gct cac aga 576
Asn Asn Ser Leu Glu Lys Glu Gln Lys Val Tyr Glu Gly Ala His Arg
160 165 170

gcg gtt gaa att gaa gct cta aca cca cac tcc agc tac tgt gta gtg 624
Ala Val Glu Ile Glu Ala Leu Thr Pro His Ser Ser Tyr Cys Val Val

175 180 185

gct gaa ata tat cag ccc atg tta gac aga aga agt cag aga agt gaa 672
Ala Glu Ile Tyr Gln Pro Met Leu Asp Arg Arg Ser Gln Arg Ser Glu
190 195 200

gag aga tgt gtg gaa att cca tga 696
Glu Arg Cys Val Glu Ile Pro
205 210

<210> 28
<211> 231
<212> PRT
<213> primate; surmised Homo sapiens

<400> 28
Met Met Pro Lys His Cys Phe Leu Gly Phe Leu Ile Ser Phe Phe Leu
-20 -15 -10

Thr Gly Val Ala Gly Thr Gln Ser Thr His Glu Ser Leu Lys Pro Gln
-5 -1 1 5 10

Arg Val Gln Phe Gln Ser Arg Asn Phe His Asn Ile Leu Gln Trp Gln
15 20 25

Pro Gly Arg Ala Leu Thr Gly Asn Ser Ser Val Tyr Phe Val Gln Tyr
30 35 40

Lys Ile Tyr Gly Gln Arg Gln Trp Lys Asn Lys Glu Asp Cys Trp Gly
45 50 55

Thr Gln Glu Leu Ser Cys Asp Leu Thr Ser Glu Thr Ser Asp Ile Gln
60 65 70 75

Glu Pro Tyr Tyr Gly Arg Val Arg Ala Ala Ser Ala Gly Ser Tyr Ser
80 85 90

Glu Trp Ser Met Thr Pro Arg Phe Thr Pro Trp Trp Glu Thr Lys Ile
95 100 105

Asp Pro Pro Val Met Asn Ile Thr Gln Val Asn Gly Ser Leu Leu Val
110 115 120

Ile Leu His Ala Pro Asn Leu Pro Tyr Arg Tyr Gln Lys Glu Lys Asn
125 130 135

Val Ser Ile Glu Asp Tyr Tyr Glu Leu Leu Tyr Arg Val Phe Ile Ile
140 145 150 155

Asn Asn Ser Leu Glu Lys Glu Gln Lys Val Tyr Glu Gly Ala His Arg
160 165 170

Ala Val Glu Ile Glu Ala Leu Thr Pro His Ser Ser Tyr Cys Val Val
175 180 185

Ala Glu Ile Tyr Gln Pro Met Leu Asp Arg Arg Ser Gln Arg Ser Glu

190 195 200

Glu Arg Cys Val Glu Ile Pro
205 210

<210> 29
<211> 693
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:reverse
translation

<220>
<221> misc_feature
<222> (1)..(693)
<223> n may be a, c, g, or t

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ttycayaaya thytncartg gcarccnggn mgngcnytna cnggnaayws nwsngtntay 180

ttygtncart ayaarathta yggncarmgn cartggaara ayaargarga ytgytggggn 240

acncargary tnwsntgyga yytnacnwsn garacnwsng ayathcarga rccntaytay 300

ggnmgngtnm gngcngcnws ngcnggnwsn taywsngart ggwsnatgac nccnmgntty 360

acnccntggt gggaracnaa rathgayccn ccngtnatga ayathacnca rgtnaayggn 420

wsnytnytng tnathytnca ygcnccnaay ytnccntaym gntaycaraa rgaraaraay 480

gtnwsnathg argaytayta ygarytnytn taymgngtnt tyathathaa yaaywsnytn 540

garaargarc araargtnta ygarggngcn caymgngcng tngarathga rgcnytnacn 600

ccncaywsnw sntaytgygt ngtngcngar athtaycarc cnatgytnga ymgnmgnwsn 660

carmgnwsng argarmgntg ygtngarath ccn 693

<210> 30
<211> 526
<212> DNA
<213> primate; surmised Homo sapiens

<220>
<221> CDS
<222> (1)..(390)

<220>
<221> mat_peptide

<222> (64)..(390)

<400> 30
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Met Met Pro Lys His Cys Phe Leu Gly Phe Leu Ile Ser Phe Phe Leu
-20 -15 -10

act ggt gta gca gga act cag tca acg cat gag tct ctg aag cct cag 96
Thr Gly Val Ala Gly Thr Gln Ser Thr His Glu Ser Leu Lys Pro Gln
-5 -1 1 5 10

agg gta caa ttt cag tcc cga aat ttt cac aac att ttg caa tgg cag 144
Arg Val Gln Phe Gln Ser Arg Asn Phe His Asn Ile Leu Gln Trp Gln
15 20 25

cct ggg agg gca ctt act ggc aac agc agt gtc tat ttt gtg cag tac 192
Pro Gly Arg Ala Leu Thr Gly Asn Ser Ser Val Tyr Phe Val Gln Tyr
30 35 40

aaa ata tat gga cag aga caa tgg aaa aat aaa gaa gac tgt tgg ggt 240
Lys Ile Tyr Gly Gln Arg Gln Trp Lys Asn Lys Glu Asp Cys Trp Gly
45 50 55

act caa gaa ctc tct tgt gac ctt acc agt gaa acc tca gac ata cag 288
Thr Gln Glu Leu Ser Cys Asp Leu Thr Ser Glu Thr Ser Asp Ile Gln
60 65 70 75

gaa tct tat tac ggg agg gtg agg gcg gcc tcg gct ggg agc tac tca 336
Glu Ser Tyr Tyr Gly Arg Val Arg Ala Ala Ser Ala Gly Ser Tyr Ser
80 85 90

gaa tgg agc atg acg ccg cgg ttc act ccc tgg tgg gaa aga gca aaa 384
Glu Trp Ser Met Thr Pro Arg Phe Thr Pro Trp Trp Glu Arg Ala Lys
95 100 105

ggt tta tgaaggggct cacagagcgg ttgaaattga agctctaaca ccacactcca 440
Gly Leu

gctactgtgt agtggctgaa atatatcagc ccacgttaga cagaagaagt cagagaagtg 500

aagagagatg tgtggaaatt ccatga 526

<210> 31
<211> 130
<212> PRT
<213> primate; surmised Homo sapiens

<400> 31
Met Met Pro Lys His Cys Phe Leu Gly Phe Leu Ile Ser Phe Phe Leu
-20 -15 -10

Thr Gly Val Ala Gly Thr Gln Ser Thr His Glu Ser Leu Lys Pro Gln
-5 -1 1 5 10

Arg Val Gln Phe Gln Ser Arg Asn Phe His Asn Ile Leu Gln Trp Gln
15 20 25

Pro Gly Arg Ala Leu Thr Gly Asn Ser Ser Val Tyr Phe Val Gln Tyr
30 35 40

Lys Ile Tyr Gly Gln Arg Gln Trp Lys Asn Lys Glu Asp Cys Trp Gly
45 50 55

Thr Gln Glu Leu Ser Cys Asp Leu Thr Ser Glu Thr Ser Asp Ile Gln
60 65 70 75

Glu Ser Tyr Tyr Gly Arg Val Arg Ala Ala Ser Ala Gly Ser Tyr Ser
80 85 90

Glu Trp Ser Met Thr Pro Arg Phe Thr Pro Trp Trp Glu Arg Ala Lys
95 100 105

Gly Leu

<210> 32
<211> 390
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:reverse translation

<220>
<221> misc_feature
<222> (1)..(390)
<223> n may be a, c, g,or t

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ggnacncarw snacncayga rwsnytnaar ccncarmgng tncarttyca rwsnmgnaay 120

ttycayaaya thytncartg gcarccnggn mgngcnytna cnggnaayws nwsngtntay 180

ttygtncart ayaarathta yggncarmgn cartggaara ayaargarga ytgytggggn 240

acncargary tnwsntgyga yytnacnwsn garacnwsng ayathcarga rwsntaytay 300

ggnmgngtnm gngcngcnws ngcnggnwsn taywsngart ggwsnatgac nccnmgntty 360

acnccntggt gggarmgngc naarggnytn 390